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HISTOPLASMOSIS IN MAN

REPORT OF SEVEN CASES AND A REVIEW OF SEVENTY-ONE CASES

ROBERT J. PARSONS, M.D., AND C. J. D. ZARAFONETIS, M.D.

ANN ARBOR, MICH.

Histoplasmosis for many years was believed to be a rare tropical disease. Twenty years elapsed between the description by Darling [1] of 3 cases which he had found in 1905 and 1906 and the next diagnosis, which was made by Riley and Watson [2] in 1926. During the past decade the disease has been found widespread in the United States and in widely scattered places throughout the world. As an indication of the frequency of occurrence of histoplasmosis we have the fact that 9 cases originating in Michigan were discovered between November 1938 and December 1940.

It is the purpose of this paper to report the 5 cases of histoplasmosis which have been observed at the University of Michigan Hospital, 1 case that originated in Ohio but was diagnosed in the Department of Pathology of the University of Michigan, and 1 case that was diagnosed by Dr. Paul Steiner of the department of pathology of the University of Chicago. Brief mention will be made of several cases which have not yet been published and the available literature will be reviewed with particular reference to the clinical aspects of the disease.

Darling was the first to describe histoplasmosis as a disease. Working in Panama, he found his first case in December 1905,[1a] and 2 more cases during 1906.[1c] While Strong [3] has sometimes been credited with describing the first case of the disease, he himself [4] at present is of the opinion that the case which he described was one of those unusual instances of the infection of man with Cryptococcus farciminosus, the fungus causing epizootic farcy in horses.[5] Darling characterized the disease as one in which there were irregular fever, emaciation and splenomegaly. Small encapsulated organisms resembling Leishman-Donovan bodies could be found in the tissues, particularly in the cells of the reticuloendothelial system.[6] He described the organism as a protozoon and named it Histoplasma capsulatum. Sections from Darling's cases were studied by Rocha-Lima [7] in 1912, and it was his opinion that the organism was a yeastlike fungus rather than a protozoon; a fungus which, as seen in the tissues, closely resembled Cryptococcus farciminosus. Confirmation of the fungous origin of the disease did not come until 1932, when DeMonbreun [8] succeeded in growing the causative fungus from the blood stream and the spleen of a 5 month old infant. Hansmann and Schenken [9] had culti-

From the Department of Pathology and the Department of Medicine, University of Michigan Medical School.

1. Darling, S. T.: (*a*) A Protozoan General Infection Producing Pseudotubercles in the Lungs and Focal Necrosis in the Liver, Spleen and Lymph Nodes, J. A. M. A. **46**:1283 (April 28) 1906; (*b*) Notes on Histoplasmosis: A Fatal Disorder Met with in Tropical America, Maryland M. J. **50**:125 (April) 1907; (*c*) A Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America, Arch. Int. Med. **2**:107 (Sept.) 1908.

2. Riley, W. A., and Watson, C. J.: (*a*) Darling's Histoplasmosis in the United States: The Possibility of Further Occurrence of Cases, Minnesota Med. **9**:97 (Feb.) 1926; (*b*) Histoplasmosis of Darling: Case Originating in Minnesota, Am. J. Trop. Med. **6**:271 (July) 1926.

3. Strong, R. P.: A Study of Some Tropical Ulcerations of the Skin with Particular Reference to Their Etiology, Philippine J. Sc. **1**:91 (Jan.) 1906.

4. Strong, R. P.: Personal communication to one of us (C. Z.).

5. Nègre, L., and Bridré, J.: Un cas de lymphangite épizootique chez l'homme. Traitement et guérison par le "606," Bull. Soc. path. exot. **4**:384 (May) 1911.

6. Darling, S. T.: The Morphology of the Parasite (Histoplasma Capsulatum) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. **11**:515 (July) 1909.

7. da Rocha-Lima, H.: Beitrag zur Kenntnis der Blastomykosen: Lymphangitis epizootica und Histoplasmosis, Centralbl. f. Bakt. (Abt. 1) **67**:233, 1913.

8. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93 (March) 1934.

9. Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus Sepedonium, Am. J. Path. **10**:731 (Nov.) 1934; A Unique Infection in Man with a New Yeast-Like Organism, ibid. **9**:925 (Nov.) 1933.

vated the organism in another case a few months earlier. They mentioned that the fungus resembled Histoplasma capsulatum but suggested that it be classified in the genus Sepedonium.

Histoplasma capsulatum occurs in the tissues in the form of small round or oval yeastlike bodies, which in our cases have measured from 1 to 5 microns in cross section, the average being approximately 3 microns. Similar measurements have been found by others.[10] They show a sharply defined, clear, achromatic capsule. The chromatin mass in the center of the organisms is irregular in distribution,[6] and in ordinary stains it usually shows a round vacuole located in the widest part of the cell. The chromatin mass, exclusive of the capsule, measures 1 to 3.3 microns.[11] The organisms stain well with most common nuclear dyes; hematoxylin and eosin, the Masson trichrome stain and the Giemsa stain are among the best combination stains for identifying them in tissues; Giemsa and Wright stains as well as supravital stains are satisfactory for staining the organisms in the peripheral blood or sternal bone marrow. The organisms are weakly gram-positive and slightly acid-fast. This is stated thus because with each of these technics great numbers of the organisms are completely decolorized.[12]

The organism will grow on most of the usual mediums, but since it grows slowly it is frequently difficult to isolate from contaminating organisms. On mediums which contain considerable protein, such as blood or serum agar and Loeffler's medium, inoculation of the yeastlike form results in growth of the yeastlike form if incubation is at 37 C. At room temperature the fungus rapidly reverts to the mycelial form on all culture mediums.[8] DeMonbreun found that he could not convert a well established mycelial form of the fungus to the yeastlike form by cultural means,[8] but Conant [13] has found that by inoculating the mycelial form on a tightly sealed blood agar slant and incubating at 37 C., conversion to the yeastlike form is brought about. Conversion of the mycelial to the yeastlike form was brought about by Negroni [14a] by culture of the mycelial form on blood agar after previous incubation at 37 C. in weak solutions of sodium hydroxide (0.01 to 0.05 per cent) or sodium borate (0.5 to 2 per cent). Conversion of the mycelial form to the yeastlike form is accomplished easily by injection of the former into any one of several laboratory animals: i. e., dogs and monkeys,[8] guinea pigs,[14] mice,[15] rats [9] and rabbits.[16] In animals, an acute or chronic, localized or widely disseminated infection is produced by varying the dose injected and the route of administration.[15]

The infection manifests itself in many different ways, as evidenced by the following case reports and the subsequent review of the literature.

REPORT OF CASES

CASE A (case 24, table).—E. G., a 63 year old white Swiss-born waiter, who had lived in Detroit, Mich., for many years, had apparently been well until January 1938. He then noted the onset of loss of weight associated with extreme nervousness. There had been no chills, fever, sweats, hemoptysis or pain in the chest, but dyspnea occurred with slight exertion. Occasional cough was attributed to postnasal drip. In June a diagnosis of diabetes mellitus was made. Treatment was instituted, but loss of weight continued, with a decline from 190 to 120 pounds (85 to 54 Kg.) by the time he was seen in the outpatient department of the University Hospital on Sept. 29, 1938.

On physical examination the patient was found to be emaciated, poorly developed and acutely ill. The temperature was 99 F., the pulse rate 88, the respiratory rate 20 and the blood pressure 120 systolic and 70 diastolic. The skin was warm, dry and dehydrated. A small, well healed perforation of the nasal septum was seen. The lips were cyanotic, dry and cracked. Oral hygiene was poor; the breath was foul, and the remaining teeth were carious, with marked pyorrhea alveolaris. The pharynx and tonsils were hyperemic and covered with thick whitish exudate. The patient complained of pain on talking and when the tongue was depressed. There was tenderness over the tonsillar and laryngeal areas. A small lymph node was palpable in the right posterior cervical region. The thorax was strikingly emphysematous, and moist, squeaky rales were heard on auscultation. The liver was palpable 5 fingerbreadths below the right costal margin and the spleen 2 fingerbreadths below the left. Tremor of the hands, cyanosis of the nailbeds and a mild bilateral foot drop were present. The reflexes were slightly hyperactive.

The results of laboratory studies were as follows: The Kahn reaction of the blood was negative. The

10. (*a*) Dodd, K., and Tompkins, E. H.: A Case of Histoplasmosis of Darling in an Infant, Am. J. Trop. Med. **14**:127 (March) 1934. (*b*) Darling.[6] (*c*) Hansmann and Schenken.[9]

11. (*a*) Crumrine, R. M., and Kessel, J. F.: Histoplasmosis (Darling) Without Splenomegaly, Am. J. Trop. Med. **11**:435 (Nov.) 1931. (*b*) Darling.[6] (*c*) Case D of this paper.

12. Parsons, R. J.: Experimental Histoplasmosis in Mice, Arch. Path. **34**:229 (July) 1942.

13. Conant, N. F.: Cultural Study of Life Cycle of Histoplasma Capsulatum, Darling 1906, J. Bact. **41**:536 (May) 1941.

14. (*a*) Negroni, P.: Estudio micológico del primer caso sud-americano de histoplasmosis, Rev. d. Inst. bact., Buenos Aires **9**:239 (June) 1940. (*b*) Redaelli, P., and Ciferri, R.: Studii sull' Histoplasma capsulatum, Darling: I. Riproduzione sperimentale della istoplasmosi e definizione della malattia nelle reticolo-istiocitosi parassitarie sistemiche, Bol. Soc. ital. d. biol. sper. **9**: 1001, 1934.

15. Tager, M., and Liebow, A. A.: Observations on Histoplasmosis: Induced Infection in the Mouse, Yale J. Biol. & Med. **14**:469 (May) 1942. De Monbreun.[8] Parsons.[12]

16. Hansmann and Schenken.[9] Redaelli and Ciferri.[14b]

hemoglobin content varied from 70 to 84 per cent (Sahli), the red blood cells from 4,110,000 to 4,930,000 per cubic millimeter, and the white blood cells from 3,400 to 5,900 per cubic millimeter. A typical differential count showed 57 per cent polymorphonuclear neutrophils, 3 per cent eosinophils, 24 per cent large lymphocytes and 16 per cent monocytes.

On four occasions albuminuria (1 to 2 plus) was noted. There was no glycosuria on five examinations. Terminally the urinary sediment was loaded with granular casts.

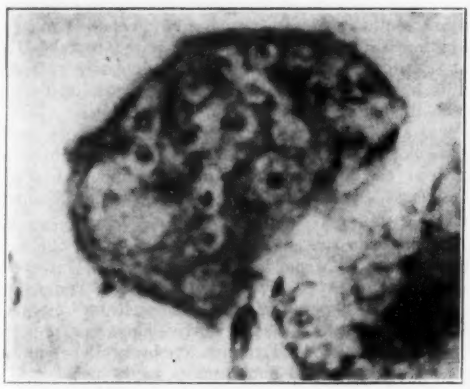

Fig. 1.—A large mononuclear phagocyte heavily parasitized by the yeastlike form of Histoplasma capsulatum. The section was made from one of the adrenals in case A (case 24 in the table). (Hematoxylin and eosin; × 1,860.)

Roentgenograms of the chest showed what appeared to be a tuberculous infiltration of the left upper pulmonary field and involvement of both upper pulmonary fields by minute parenchymal infiltrations, suggesting a lesion of miliary type. Acid-fast organisms typical of Mycobacterium tuberculosis were found in the sputum. The total serum protein was 6.6 Gm. per hundred cubic centimeters, with 2.9 Gm. albumin, and 3.7 Gm. globulin. A dextrose tolerance test showed a curve of diabetic type. A faint trace of dextrose was present in the specimen of urine taken at the third hour. On the day of the patient's death the fasting blood sugar content was 121 mg. per hundred cubic centimeters and the nonprotein nitrogen content 103.4 mg.

The patient was treated in the outpatient department until the positive result of examination of the sputum was reported, on October 18, when he was admitted as an inpatient. His condition rapidly became worse. Throughout his hospitalization his temperature was intermittently elevated, ranging from 98 to 102.8 F. Swallowing became extremely difficult and painful, finally necessitating intravenous administration of fluids. After the development of cyanosis and coma, death occurred on November 25.

The pertinent observations at necropsy were as follows: There was extensive fibrocaseous tuberculosis with cavity formation in the upper lobe of the left lung. Great numbers of tubercle bacilli were readily stained in the walls of the cavities. Miliary tubercles were found in the pituitary gland, thyroid, tongue, pharynx, larynx, lungs, bronchial lymph nodes, kidneys, prostate and small intestine. The liver weighed 1,540 Gm. and contained many miliary tubercles. The spleen weighed 470 Gm. and histologically showed great numbers of relatively recent miliary tubercles. The kidneys weighed 170 and 180 Gm. and showed relatively acute patchy tuberculous nephritis.

The adrenals were greatly enlarged, one weighing 50 and the other 60 Gm. There was almost complete caseation necrosis of both. The granulation tissue surrounding the areas of caseation necrosis and in the periadrenal fat consisted of young fibroblasts in the meshes of which were many large mononuclear phagocytes. The cytoplasm of these phagocytes contained round or oval bodies (fig. 1) measuring from 2 to 5 microns in diameter. Stained with hematoxylin and eosin, these bodies showed a clear achromatic capsule within which was an oval, weakly basophilic chromatin mass. In most instances an almost spherical, clear vacuole could be seen in the chromatin mass. The vacuole was eccentrically placed, but in those organisms which were oval or piriform it was located in the widest part of the yeastlike cell. The organisms were slightly acid-fast and alcohol-fast and weakly gram-positive.

There was a punched-out ulcer on the tongue, 1 cm. in diameter. An ulcer in the hypopharynx measured 2.5 by 0.6 cm. and was 3 mm. deep. From the ileocecal valve to the rectum there were approximately twenty punched-out ulcers, 8 to 12 mm. in diameter. A few Histoplasma capsulatum organisms were found in macrophages in the granulation tissue base of ulcers in each of these regions.

Extended search for similar organisms in all of the other organs of the body proved futile. None were found in the miliary tubercles, which were widely disseminated throughout the body. Carefully controlled acid-fast stains failed to reveal anything resembling Mycobacterium tuberculosis in these tubercles or in the caseous adrenal glands. No cultures were made of the adrenal tissue, and postmortem cultures of blood showed no significant growth.

A diagnosis of histoplasmosis of the adrenals was made on December 1, but it was not until several months later that the organisms were found in the

Fig. 2.—Ulcerated granulomatous lesion in case B (case 37 in the table). The granuloma had caused perforation of the nasal septum. Histoplasmosis was diagnosed by biopsy and by culture of the lesion. (× 1.)

glossal, pharyngeal and colonic ulcers. Since fibrocaseous tuberculosis with cavity formation was present in the lungs, the pathogenesis of the widespread miliary tubercles remains obscure. Neither Histoplasma capsulatum nor Mycobacterium tuberculosis could be stained in these lesions.

CASE B (case 37, table).—N. C., a 25 year old white woman, a native of Michigan, was admitted to the University Hospital on Aug. 30, 1939, with hem-

orrhage from the rectum as the chief complaint. She had been seen there previously, in 1935, at which time a diagnosis of Cushing's syndrome was made.

One year prior to readmission she noted swelling and ulceration of the nose. Septal perforation resulted in two months, but thereafter the lesion was apparently stationary. A purulent, foul-smelling discharge was present continuously. On June 1, 1939, a large amount of blood was expelled by rectum, and several similar episodes occurred subsequently. Weakness, dyspnea and generalized abdominal discomfort followed the repeated hemorrhages.

Physical examination revealed an obese female who appeared chronically ill. The temperature was 99.6 F., the pulse rate 108 and the respiratory rate 16 per minute. The blood pressure was 138 systolic and 94 diastolic. The classic signs of Cushing's syndrome, except the severe anemia, were present. A granulating ulcerative process had partially destroyed the right naris (fig. 2). This lesion extended onto the upper lip, and a septal perforation was present with slight involvement of the mucous membrane of the left naris. A purulent exudate could be seen on the ulcerated surfaces. Several ulcerations about the gums and one on the roof of the mouth were also seen. There was no palpable lymphadenopathy, and the liver and spleen could not be felt.

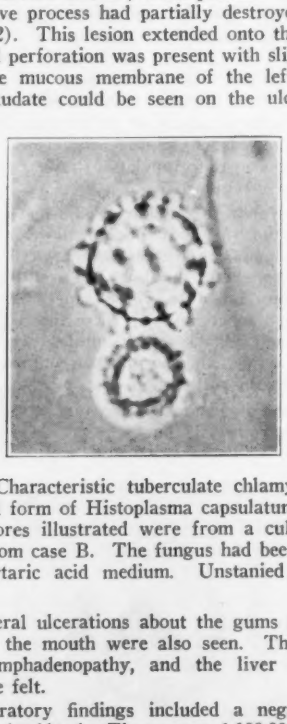

Fig. 3.—Characteristic tuberculate chlamydospore of the mycelial form of Histoplasma capsulatum. The two chlamydospores illustrated were from a culture of the organism from case B. The fungus had been grown on dextrose-tartaric acid medium. Unstanied; × 1,860.)

The laboratory findings included a negative Kahn reaction of the blood. There were 1,100,000 red blood cells per cubic millimeter, and the hemoglobin content was 20 per cent (Sahli). The white blood cell count was 2,200 per cubic millimeter, and the differential count, 69 per cent neutrophils, 27 per cent lymphocytes and 4 per cent monocytes. Leukopenia persisted throughout the period of observation. Roentgenographic studies of the chest and the gastrointestinal tract did not reveal anything abnormal, nor did sigmoidoscopic examination. Histologic examination of a specimen from the nasal lesion revealed granulomatous tissue containing enormous numbers of large mononuclear phagocytic cells filled with organisms morphologically similar to Histoplasma capsulatum, and a diagnosis of histoplasmosis was made. On the following day a small amount of tissue was removed from the ulcer for culture. From this material the mycelial form of Histoplasma capsulatum was isolated in broth by Dr. Walter Nungester and on dextrose–tartaric acid medium by Miss Helen Pellet. The characteristic tuberculate chlamydospore (fig. 3) of the fungus was easily identified in these cultures. The organisms were not demonstrated in the peripheral blood or sternal marrow, and repeated blood cultures showed no growth.

While the patient was in the hospital, an irregular pyrexia was present, the temperature reaching as high as 102.4 F. Following repeated blood transfusions, her general condition was improved, and she was discharged, no change having occurred in the nasal lesion. Another episode of gross intestinal bleeding occurred shortly thereafter. The patient was followed in the outpatient clinic, where she was treated with weekly injections of 0.3 Gm. of neoarsphenamine; no noticeable benefit resulted from four such treatments. This was discontinued, and the patient was advised to take 0.32 Gm. of thymol daily. The liver was easily palpable at this time. She did not return to the hospital during the month before her death, on Nov. 21, 1939. While she was at home there had been no further gross intestinal hemorrhage, and although the nasal lesion appeared improved, the lesions of the gums and mouth had become worse. Permission for autopsy was not obtained.

Case C (case 47, table).—A. J. W., a 41 year old white American salesman, was admitted to the Thomas Henry Simpson Memorial Institute of the University of Michigan on Aug. 6, 1940, with the chief complaints of fever and weakness. He had been well until eighteen months prior to admission, when enlargement of the neck was first noted. Examination by his local physician revealed enlarged lymph nodes in the neck, axillas and inguinal regions. On March 30, 1939, a lymph node in the right supraclavicular region was removed for biopsy. After a series of roentgen ray irradiations, the glands regressed so as to become unnoticeable, and the patient felt well and was ambulatory until June 17, 1940. At that time an infection of the upper respiratory tract developed, which persisted for a week. There were ease of fatigue, weakness and a dry, hacking cough. Shortly thereafter fever, profuse diaphoresis, anorexia and abdominal distention developed and persisted to the time of his admission to the hospital. A loss of weight of 30 pounds (13.5 Kg.) occurred during the same interval.

On physical examination the temperature was 101.6 F., the pulse rate 88, the respiratory rate 22 and the blood pressure 116 systolic and 58 diastolic. The patient was well developed and well nourished and appeared subacutely ill. The skin was flushed, warm and moist. A few small posterior cervical lymph nodes were felt. A single discrete, soft, nontender node was felt in each axilla, and several inguinal nodes were palpable. The thorax was symmetric and expanded equally on the two sides. The lungs were resonant throughout, but on auscultation the breath sounds were harsh and bronchial in quality. Rales were present throughout; sharp, high-pitched squeaks were heard in the right lower pulmonary field posteriorly on deep inspiration. The abdomen was distended, and there was considerable tenderness in the right upper quadrant. The liver extended 7 cm. below the costal margin, and the spleen was palpable 3 cm. below the left costal margin.

Laboratory studies gave the following results: The Kahn reaction of the blood was negative. The hemoglobin content declined from 85 to 75 per cent, while the red blood cell count fell from 5,000,000 to 4,000,000 per cubic millimeter; the white blood cell count ranged from 2,650 to 9,550 per cubic millimeter. A representative differential count showed 76 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 16 per cent lymphocytes and 7 per cent monocytes. On the day of death the reticulocytes numbered 6.5 per cent, and 1 of every thousand red cells was nucleated. Five analyses of

the urine and two of the stool gave essentially negative results.

A microscopic section, prepared at another hospital, from the lymph node removed in 1939 was examined by the department of pathology. A diagnosis of lymphoblastoma of lymphosarcoma type was made, confirming the diagnosis previously made at the other hospital.

Roentgenograms revealed hilar parenchymal changes compatible with the clinical diagnosis of lymphoblastoma. Reexamination of the chest two days before the patient's death showed a considerable increase in the prominence of each hilar shadow and disseminated patchy infiltration of both lungs. It was thought most probably to be due to advance of the lymphoblastoma, although the roentgenologist stated that a disseminated bronchopneumonia associated with extensive lymphadenopathy could produce a similar picture.

During his stay in the hospital the patient became progressively worse. His temperature was irregularly elevated to almost 104 F. daily, but during the last four days it fell to near normal levels. The pulse and respiratory rates showed a gradual and continual rise. Roentgen therapy was instituted, the patient receiving 400 r to each of eight ports about the chest and retroperitoneal region without appreciable symptomatic change. Weakness became more pronounced, patchy consolidation of the lungs developed and death occurred on Aug. 26, 1940.

After a necropsy a review of the daily blood films revealed the presence of the characteristic yeast form of Histoplasma capsulatum in the blood films made during the last two days of life, but not in those made on previous days. The organisms were found in many of the polymorphonuclear leukocytes (fig. 4) and could not be found in the other white blood cell elements.

At necropsy the external features were much as described. Moderate edema was present in the feet.

The lungs were more voluminous than usual, the left weighing 950 Gm. and the right 1,070 Gm. The pleural surfaces were smooth, moist and shiny except at the apexes, where depressed gray scars were present. The parenchyma was firm but somewhat aerated in spite of the firmness. The cut surfaces were grayish red and firm. On pressure some edema fluid exuded from the surface and grayish mucoid material was found in the bronchi. No tumor masses could be made out. There was slight congestion of the bronchial mucosa. The anthracotic pigmentation of the bronchial lymph nodes in some places gave way to grayish-red streaked areas, but there was no notable enlargement of these nodes. Microscopically, lung sections stained with hematoxylin and eosin and with the Masson trichrome stain showed a widespread subacute pneumonitis. This was characterized by the presence of polymorphonuclear cells, large mononuclear phagocytes and masses of old fibrin in the alveoli. The large mononuclear phagocytes contained numerous small encapsulated organisms morphologically like Histoplasma capsulatum. Many of the alveoli were lined with a single layer of flattened cells which could be easily distinguished from the endothelium of the capillaries in the alveolar walls. Organisms were not found in these cells. In a few places organization of the alveolar exudate was seen. Other areas gave evidence of chronic pulmonary edema, and in still others there were acute pulmonary abscesses in which postmortem colonies of cocci were interspersed with the fibrinopurulent exudate. There was hyalinization of dense fibrous pleural and parenchymal scars in the apexes. The bronchi and bronchioles showed an acute fibrinopurulent exacerbation of a chronic bronchitis.

Microscopically, the bronchial lymph nodes revealed an almost complete loss of the usual follicular architecture. The peripheral sinuses and the sinusoids were packed with large mononuclear phagocytes parasitized by great numbers of small encapsulated organisms, and similar cells were seen in the capsule of the nodes. There were numerous areas of necrosis surrounded by heavily parasitized phagocytes and fibrous connective tissue in the nodes. Apparently inactive fibrocaseous tubercles also were present.

The liver was nearly twice the normal size, weighing 2,960 Gm. Its capsule was everywhere smooth and glistening. The yellowish color of the cut surface suggested lipidosis. Microscopically, the liver showed far advanced fatty infiltration. In many of the portal spaces there were small lymphocytes in increased numbers, and some were widened by these cells together with a few large mononuclear phagocytes. The latter contained Histoplasma capsulatum in their cytoplasm. In one area this type of cellular infiltration appeared to extend beyond the bounds of the portal spaces into the hepatic parenchyma. Organisms were found in a few Kuppfer cells.

Great enlargement of the spleen had occurred, its weight being 620 Gm. The capsule had a purplish color, and a dark red mottling on a purplish background was seen on the cut surface. The pulp was firm. Microscopic sections revealed evidence of marked chronic passive congestion. Parasitized large mononuclear phagocytes were seen singly and in small groups among the lymphocytes in the splenic corpuscles.

Fig. 4.—Photograph of a polymorphonuclear neutrophil in a blood smear made in case C (case 47 in the table). Two of the yeastlike forms are seen within the cytoplasm of the neutrophil. (Wright's stain; × 1,380.)

Both kidneys were somewhat enlarged, the right weighing 200 and the left 220 Gm. The only apparent gross pathologic change was slight pallor. In sections many of the intertubular capillaries contained large numbers of polymorphonuclear cells and normoblasts.

The adrenal glands were normal in appearance grossly, but microscopically each contained a few parasitized reticuloendothelial cells in the cortical capillaries and sinusoids.

In the region of the ileocecal valve there was hyperplasia of the lymphoid follicles. Large numbers of parasitized large mononuclear phagocytes were seen in this lymphoid tissue. Among the lymphocytes in the gastric mucosa a few parasitized mononuclear cells were present. The same was true of the appendix.

The mesenteric and retroperitoneal lymph nodes were enlarged and revealed small areas of necrosis. They were rather friable. Histologically, the changes in them resembled those described in the bronchial nodes.

The bone marrow from the sternum, a rib and a vertebral body was hyperplastic. A few parasitized

reticuloendothelial cells were found in the bone marrow from a rib and a vertebral body.

None of the sections revealed the most remote suggestion of a lymphosarcoma or other neoplasm, and it is our belief that the sections sent us by another hospital which were said to have come from this patient actually were from another patient.

CASE D (case 53, table).—D. P., a 49 year old white printer, was admitted to the Simpson Memorial Institute on Dec. 25, 1940. He had lived in many states during his life, but for the past two years he had lived in the upper peninsula of Michigan. For nine months prior to admission he had noted malaise and anorexia. In June 1940 he experienced severe pain in the right ear which persisted several weeks and then disappeared spontaneously. In August a small nodular lesion appeared in the left external auditory canal. One month later this was incised by his local physician, but no drainage resulted. At that time it was noted that a node in the left preauricular region was enlarged. Subsequently, nonpainful granulomatous oral lesions appeared. During the two month period preceding hospitalization, fever and night sweats became an almost daily occurrence, and there were progressive weakness, malaise and loss of weight.

His local physician took tissue specimens from the lesions of the left ear and the pharynx in December 1940. These were sent to the University of Michigan department of pathology, where the diagnosis of histoplasmosis of Darling was made.

On physical examination, the patient was seen to be well developed but appeared chronically ill and emaciated. His temperature was 98.2 F., his pulse rate 80, his respiratory rate 20 and his blood pressure 88 systolic and 62 diastolic. The skin was loose, revealing evidence of recent loss of weight. On the posterior wall of the right external auditory canal there was a raised granular mass partially occluding the lumen. A similar but larger nodule was present in the left auditory canal. Granulation tissue was present also around a right molar tooth, behind the lower front teeth and on the right posterior tonsillar pillar. The right tonsil was moderately enlarged. The thorax was normal. The abdomen was scaphoid, muscular and difficult to palpate. However, the liver and spleen were each felt 2 finger-breadths below the costal margin. Generalized lymphadenopathy was noted, with involvement of anterior auricular, submaxillary, submental, occipital, anterior and posterior cervical, axillary and inguinal nodes. Some of these nodes were tender.

The laboratory findings included the following: The Kahn reaction of the blood was negative. The red blood cell count was 5,000,000 per cubic millimeters and the hemoglobin content 85 per cent (Sahli). The white blood cell count varied from 4,250 to 5,750 per cubic millimeter, a typical differential count showing 70 per cent polymorphonuclear cells, 3 per cent eosinophils, 18 per cent lymphocytes and 9 per cent monocytes. The total serum protein was 8.2 Gm. per hundred cubic centimeters, with 3.9 Gm. of albumin, and 4.3 Gm. of globulin. The serum bilirubin content was 0.66 mg. per hundred cubic centimeters, and the icteric index ranged from 2 to 5. The sedimentation rate was 26 mm. per hour (Wintrobe). Sternal aspiration revealed a few extracellular organisms believed to be Histoplasma capsulatum. Lymph nodes were obtained for section, animal inoculation and cultural studies. The sections showed many phagocytes filled with Histoplasma capsulatum. Young mice were inoculated[12] intravenously with ground suspensions of the lymph nodes. All died with histoplasmosis. Culture of the nodes on blood agar slants at 37.5 C. yielded the yeastlike form of Histoplasma capsulatum. Cultures of the nodes on Sabouraud's medium yielded pure cultures of the mycelial form of the same organism. All cultures of the blood were negative. Daily blood films failed to reveal organisms at any time. Roentgen examination of the chest revealed nothing abnormal.

The patient was treated with graduated doses of neostam,[17] a pentavalent antimony preparation, given intravenously. After a total of 0.56 Gm. had been administered, this therapy was discontinued because of toxic reactions manifested by nausea, vomiting, severe prostration and what appeared to be an early stomatitis. Sodium thiosulfate in 10 per cent solution was then given intravenously, 10 to 30 cc. daily, a total of 14.5 Gm. being administered during the course of nine days. Treatment was without avail, and the symptoms present on admission gradually increased. The temperature ranged up to from 99.5 to 101.5 F. daily. Within a short period the patient became stuporous, and on Jan. 20, 1941, respirations ceased.

At autopsy, peripheral lymphadenopathy such as had been described clinically was present. The peripheral lymph nodes were enlarged to as much as 1 cm. in diameter. They were firm and freely movable. In addition, tracheobronchial, mesenteric and retroperitoneal lymph nodes were enlarged to as much as 3 cm. in diameter. A few of them showed small, irregular, creamy yellow areas of caseation necrosis.

The right tonsil was moderately enlarged and showed a creamy yellow, chronically ulcerated surface. The remainder of the tonsillar tissue was moist, gray and finely granular in appearance. The mucous membrane of the pharynx, the posterior surface of the tongue, both surfaces of the epiglottis and the mucosa of the larynx showed dome-shaped gray nodules from 1 to 5 mm. in diameter and elevated 1 to 3 mm. The central portion of several of these revealed small irregular yellow areas of necrosis. Microscopic sections of these lesions showed a granulation tissue containing great numbers of large mononuclear phagocytes. The phagocytes were heavily parasitized by the yeastlike form of Histoplasma capsulatum.

No significant pathologic change was seen in the heart. The lungs were normal in size and shape and weighed 290 and 440 Gm. respectively. The right lung, which was the heavier, showed evidences of congestion and edema of the lower lobe. Both lungs had a fine sandy feel to palpation. The cut surface revealed ten to twenty small, firm nodules, 0.8 to 1.0 mm. across, which accounted for the sandy texture. The nodules were pale pink. Microscopically, these lesions consisted of irregularly arranged large mononuclear cells lying in a slightly vascular stroma. Numerous lymphocytes were scattered through the lesions. The centers of some of the lesions were the sites of caseation necrosis. However, the lesions did not closely resemble ordinary miliary tubercles. No acid-fast organisms could be found in them, and only one body resembling the yeast form of Histoplasma capsulatum was found after extended search. There was chronic catarrhal bronchitis. Anthracosis and an old fibrocaseous tuberculous nodule were found in the bronchial lymph nodes.

The liver was moderately and uniformly enlarged, weighing 1,900 Gm. The capsular and cut surfaces showed an unusual mottling, with wide gray-white bands of tissue separating lobules of brown liver parenchyma. Microscopically, the gray-white tissue consisted of bands of young connective tissue which filled the portal spaces, widening and distorting them. Scat-

17. Stibamine glucoside (Burroughs-Wellcome & Co., Inc., New York).

tered through this granulation tissue, moderate numbers of lymphocytes and large mononuclear phagocytes were seen. Many of the latter were parasitized by Histoplasma capsulatum.

The spleen was slightly enlarged, weighing 205 Gm. The cut surface revealed unusual prominence of the lymphoid follicles. A few of these showed small yellow areas of necrosis. Microscopically, several large mononuclear phagocytes, some of them parasitized, were seen among the lymphocytes in the malpighian corpuscles. At the periphery of some of the malpighian corpuscles, there were miliary granulomatous lesions resembling those described in the lungs and containing organisms. Caseation necrosis was present in the largest of these. There was an acute exacerbation of chronic passive congestion.

Extensive pathologic change was present in the adrenals. They were greatly enlarged, the left weighing 70 and the right 65 Gm. The surfaces were mottled gray and white, and each was very firm to palpation. The cut surfaces of each adrenal showed dense gray-white translucent strands of fibrous tissue interspersed between large, irregular, yellow areas of caseation necrosis. No normal adrenal cortex could be found. Study of microscopic sections revealed large mononuclear phagocytes lying at the margins of large areas of caseation necrosis. The phagocytes were very heavily parasitized. The organisms in the phagocytes measured from 1.8 to 4.8 microns, with an average of 2.98 by 3.3 microns, including the capsule. Excluding the capsule the range was 1.35 to 3.3 microns, with average figures of 1.68 by 1.9 microns. Cords of young fibroblastic connective tissue coursed between the areas of caseation necrosis. The adrenal capsule was fibrosed. Parasitized mononuclear phagocytes were present outside and inside the capsule. Only a few small islands of recognizable adrenal cortical tissue could be found, although many blocks of tissue were studied.

The kidneys were normal in size and shape. Microscopically, a few small nodules of granulation tissue of the type that has been described were found in the interstitial tissue. A few organisms were found in these areas.

Large chronic ulcers were found in the mucosa of the small and large intestines. Each of these had a firm, thick, rounded edge and a relatively firm base. The surface of the ulcers was gray and slightly granular. On the peritoneal surface outside the ulcers, there were firm, raised, gray-white fibrous areas. From the margins of these areas, white threadlike strands extended circumferentially beneath the serosa. In the small intestine, the long axis of the ulcers and of the fibrous plaques extended around the intestine and the threadlike strands extended radially toward the mesentery. Microscopically, the base of each ulcer consisted of chronic granulation tissue containing young fibrous connective tissue and parasitized large mononuclear cells. The thin threadlike strands seen grossly were lymphatics which were filled with the same type of granulation tissue. Grossly these ulcers closely resembled tuberculous ulcers, but acid-fast stains failed to reveal any organisms resembling Mycobacterium tuberculosis. The ulcers varied from 0.3 to 4.0 cm. in their greatest diameter. In the small intestine they were most numerous in the ileum. None was present in the duodenum.

In addition to the changes just described, small granulomatous lesions resembling those described were found in the submucosa of the appendix and in a parathyroid gland.

The yeastlike form of Histoplasma capsulatum was easily grown in pure culture from the direct smear of adrenal tissue on a blood agar plate incubated at 37 C. This was properly identified by growth of the mycelial form of the fungus.

Case E (case 71, table).—M. K., a 60 year old white American farmer, had been well until October 1942. At that time he noticed a swollen, tender area on the left side of the upper surface of his tongue. The lesion spread down over the side of the tongue to involve the floor of the mouth. Considerable pain was associated with it. About November 1, the upper lip became swollen and painful. The lesions progressed until he entered the University Hospital, Jan. 18, 1943.

Physical examination revealed a punched-out, smooth, well circumscribed ulceration on the top of the tongue which measured 2 by 3 cm. The ulcer was extremely tender when touched. Swelling of the entire upper lip was present, and on the left side there was an ulcer 4 by 1.5 cm., just within the vermilion border. This lesion was also exquisitely tender. A palpable lymph node was found in the left submaxillary region. He was edentulous and had worn dentures for twenty years. His weight on admission was 120 pounds (54 Kg.), this representing a loss of 15 pounds (7 Kg.) during the past few months. The remainder of the physical examination showed no significant variations from normal. The liver and spleen were not palpable. The blood pressure was 120 systolic and 60 diastolic, and the admission temperature was normal.

The laboratory findings during his illness were as follows: The Kahn reaction of the blood was negative repeatedly. A Kahn test of the spinal fluid and a Kline test of the blood also gave negative results. The hemoglobin content ranged from 63 to 67 per cent, and the red blood cell counts varied from 3,800,000 to 4,000,000 and the white blood cell counts from 4,050 to 9,800 per cubic millimeter. A typical differential count was polymorphonuclear neutrophils 74.5 per cent, lymphocytes 14 per cent, monocytes 10 per cent, eosinophils 0.5 per cent and basophils 1 per cent. (This patient had been in the University Hospital in 1940 with herpes zoster oticus. Red blood cell counts at that time ranged from 4,200,000 to 4,380,000 and white blood cell counts from 5,600 to 6,550. Differential counts at that time were not significantly different from that just given.) Repeated careful study of the blood smears, smears of the buffy coat from centrifuged blood and smears of a sternal marrow failed to show Histoplasma capsulatum. Vacuolation of the monocytes was noted in one of the blood smears. The urine was essentially normal until early in June, when 3 to 5 red blood cells and 10 white blood cells per high power field and a trace of albumin were found. There were similar urinary findings a few days later. The nonprotein nitrogen content was 42 mg. per hundred cubic centimeters and the serum calcium content was 9.3 mg.

A tuberculin test showed a minimal positive reaction forty-eight hours after the intracutaneous injection of a 1:100 dilution of old tuberculin. The reaction to a cutaneous test with 1:1,000 coccidioidin was negative. Cutaneous tests for histoplasmosis[18] gave negative results with dilutions of 1:10,000 and 1:1,000. Agglutination tests for tularemia and undulant fever also gave negative results.

The elevations in temperature were irregular at first. During the first two weeks the temperature was within the normal range on all except two days, when there was an elevation to 102 F. Then the temperature was

18. Zarafonetis, C. J. D., and Lindberg, R. B.: Histoplasmosis of Darling; Observations on Antigenic Properties of Causative Agent; Preliminary Report, Univ. Hosp. Bull., Ann Arbor 7:47 (June) 1941.

elevated to 101 or 102 F. daily for two weeks. Next, for a period of three weeks, the temperature was in the normal range most of the time and never rose to 100 F. After March 14 there was a daily spiking of the temperature curve, with daily return to normal or below. The peak temperatures were usually 101 or 102 F., but on a few occasions temperatures of 104 and 105 F. were attained. Associated with these high temperatures there was frequently a mild chill.

During the patient's first three weeks in the hospital, material was removed from the ulcerated areas of the lip and tongue for histologic examination and for culture and animal inoculation. The first biopsy material showed evidence of a chronic infective granuloma. No organisms were found in the sections. The lesion had many of the attributes of tertiary syphilide. The second biopsy showed the same general characteristics, but this time some of the granulation tissue had a nodose character. Acid-fast stains failed to reveal Mycobacterium tuberculosis, but the Giemsa stain revealed a few intracellular yeastlike bodies. These bodies were of much larger size and of different shape than Histoplasma capsulatum. The organisms were described, and it was stated that they might indicate a form of pathogen with which we were unfamiliar or that they might consist of secondary invaders. Histoplasma capsulatum was not seen in other biopsy specimens of the lip and tongue.

Anaerobic and aerobic cultures, cultures for tubercle bacilli and cultures for fungi were made of fresh fragments of tissue at the time of the biopsies just mentioned. These cultures, as well as many others made of smears of the ulcers and of the sputum and urine, all failed to reveal a significant pathogen. Guinea pigs inoculated with fragments of tissue and with concentrated sputum failed to show any evidence of infection.

The lesions of the lip and tongue remained approximately unchanged for several weeks. Granulomatous ulcerations developed in the pharynx and larynx during the early part of March. These were widespread and finally caused extreme dysphagia and complete aphonia. Biopsy and culture of the pharyngeal tissue revealed no clues as to the nature of the process.

Late in March there was evidence of a pneumonitis at the base of the right lung. This cleared after a few weeks, and a similar process developed at the base of the left lung in the latter part of April. A widely disseminated generalized fine granularity of both lungs, more pronounced on the right, was noted in roentgenograms early in April, but it appeared to have retrogressed somewhat by the end of the month.

Many forms of treatment were tried without avail. Mouth washes with potassium permanganate solution, swabbings with tincture of iodine and glycerine and irrigations of the throat with hot saline solution were all used to combat the oropharyngeal ulcerations. Intramuscular injections of a bismuth preparation and oral administration of potassium iodide were used. During a period of one week early in March, 6 Gm. of sulfadiazine was given each day. This did not alter the progress of the pharyngeal and laryngeal ulcers. Potassium and antimony tartrate was given intravenously in increasing amounts during two of the last three weeks of life. After the application of 900 r of roentgen radiation to the lesion of the lip and to each side of the neck, there was a subsidence of the extreme tenderness in the labial and pharyngeal lesions. During this treatment, the lesions of the lip and tongue showed considerable regression but failed to heal.

The patient's general condition gradually became worse. There was further loss of weight to 99 pounds (44.5 Kg.). The dysphagia became so severe that it was necessary to perform a gastrostomy. The liver became barely palpable on deep inspiration. Finally several transfusions of whole blood were given. After the last of these the patient appeared to go into shock. The heart rate was irregular, and an electrocardiographic tracing showed many showers of ventricular extrasystoles. Cheyne-Stokes respiration developed, and respirations ceased on July 16, 1943.

An autopsy was done one hour and fifteen minutes after death. There was nothing remarkable on external examination. The left side of the tongue showed a large ulcerated area (fig. 5), which measured 4 cm. in its greater diameter. The edges of the ulcer were rounded and smooth, while the base of the ulcer was red and smooth in appearance. On the posterior surface of the tongue there were numerous irregular, raised gray nodules which did not appear to be ulcerated. Similar nodules were seen in the mucosa of the pharynx. The tonsils were not remarkable. There was slight thickening of the epiglottis, and a granular, ulcerated area covered much of its laryngeal surface. The entire mucosa of the larynx was thickened, and its surface presented an ulcerated, gray, finely granular appearance. The vocal cords had been almost completely destroyed by the ulcerative process. The trachea showed no gross pathologic change.

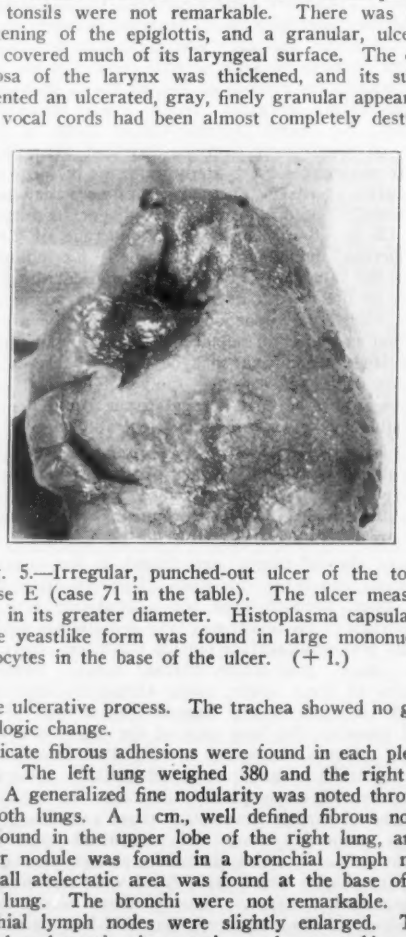

Fig. 5.—Irregular, punched-out ulcer of the tongue in case E (case 71 in the table). The ulcer measured 4 cm. in its greater diameter. Histoplasma capsulatum, in the yeastlike form was found in large mononuclear phagocytes in the base of the ulcer. (+ 1.)

Delicate fibrous adhesions were found in each pleural space. The left lung weighed 380 and the right 520 Gm. A generalized fine nodularity was noted throughout both lungs. A 1 cm., well defined fibrous nodule was found in the upper lobe of the right lung, and a similar nodule was found in a bronchial lymph node. A small atelectatic area was found at the base of the right lung. The bronchi were not remarkable. The bronchial lymph nodes were slightly enlarged. They showed anthracotic pigmentation and were rubbery.

The heart was normal in shape and weighed 320 Gm. The myocardium was flabby and of normal thickness. The chambers were of normal size. On the atrial surface of the leaflets of the tricuspid valve there were three raised, moderately firm, yellowish, verrucous vegetations. The largest of these measured 2 cm. in height and protruded into the right ventricle. The other two lesions were sessile. Except at the base of the vegetations there was no thickening of the leaflets. A small fibrous adhesion was found close to the com-

missures of two of the pulmonic cusps. The mitral and aortic valves showed only changes incident to atherosclerosis.

There was no gross abnormality of the spleen, which weighed 140 Gm. The firm liver was slightly enlarged, weighing 1,980 Gm. The mesenteric lymph nodes were not unusual. The kidneys weighed 140 and 150 Gm. The left showed three whitish subcapsular nodules approximately 1 mm. in diameter. The remainder of the organs, including the brain and a segment of the spinal cord, were without significant gross changes.

Cultures were made of material from the lesions at the base of the tongue, the ulcerated areas in the larynx and the large vegetation on the tricuspid valve.

Routine sections of the tricuspid vegetation showed large masses of fibrin attached to the ulcerated surface of the tricuspid valve. A few fibroblasts could be seen growing into the base of the vegetation, and a few large mononuclear cells, apparently phagocytes, were seen in the meshes of the fibrin near the base of the vegetation as well as in groups near its surface. No recognizable etiologic agent could be found in the routinely stained sections. However, after sections were stained with Giemsa stain, veritable colonies of small encapsulated yeastlike bodies having the size, shape and staining attributes of Histoplasma capsulatum were readily seen. These colonies were found deep in the masses of fibrin and were entirely extracellular. In these colonies a few of the organisms attained a greater size than we have previously seen, the largest being slightly oval and measuring 10.5 by 9 microns. The chromatin mass within the capsule measured 7.5 by 6.5 microns. Numerous budding forms were present. Sections of one of the smaller vegetations showed small colonies of the usual pathogenic form of Histoplasma capsulatum surrounded by thick, hyaline masses of fibrin. Some of these colonies were attached to the ulcerated surface of the valve. Others were seen between the collagen fibers of the valve, some distance below a surface that was covered by apparently normal endothelium. There was no evidence of cellular activity about these. At one point, just beneath the endothelium, numerous organisms were seen free in the tissues and not surrounded by fibrin.

Examinations of the lesions on the tongue, in the pharynx, on the epiglottis and in the larynx revealed extensive ulceration of the mucous membrane. The base of the ulcer in each case was formed by granulation tissue which consisted of moderately vascular fibroblastic connective tissue heavily infiltrated with plasma cells and lymphocytes. Protracted examination of this granulation tissue revealed a few large mononuclear phagocytes. The cytoplasm of many of these phagocytes contained one or more Histoplasma capsulatum organisms, but they were not present in the great numbers that we had seen in the earlier cases. The organisms were found most easily at the margins of the ulcers, beneath intact epithelium. None was found in the cytoplasm of the plasma cells or lymphocytes. A striking feature of several of these ulcers was the nearly complete lack of polymorphonuclear neutrophils in the granulation tissue forming the base of the ulcers. Mast cells were found in small numbers throughout the granulation tissue.

A few Histoplasma capsulatum organisms were found in large mononuclear phagocytes in the leptomeninges over the base of the brain in one section and in the wall of a small meningeal artery. A few were found in the media of the aorta and in the wall of a small adventitial artery of the aorta. These organisms did not appear to be intracellular. In the lungs numerous small nodular lesions were visible to the unaided eye in the sections. Microscopically most of these were seen to consist of small, irregularly shaped masses of connective tissue which showed heavy anthracotic pigmentation. There were a few sharply circumscribed lesions which consisted of large mononuclear phagocytes surrounded by a narrow band of lymphocytes. A few giant cells were found in the centers of the lesions. These lesions closely resembled true miliary tubercles, but stains for acid-fast bacilli revealed no tubercle bacilli and an occasional Histoplasma capsulatum organism was found in the phagocytes and in the giant cells. A few organisms were likewise found in the cytoplasm of alveolar phagocytes. One section showed a whorled fibrous scar which was believed to be the remains of a healed primary tuberculous infection. A similar healed fibrous nodule was seen in a bronchial lymph node. No identifiable organisms were found in the bronchial lymph nodes.

Small granulomatous nodules consisting of young connective tissue, moderate numbers of lymphocytes and plasma cells and a few large mononuclear phagocytes were seen in the liver and pancreas. Minute examination of these lesions revealed an occasional pale acidophilic-staining body having the size and shape of Histoplasma capsulatum, but they could not be definitely identified as such. A few Histoplasma capsulatum organisms were found in the cytoplasm of a small group of mononuclear cells in the wall of one of the ureters, and a few were found in the bone marrow from a rib. No organisms were found in the pancreas, spleen or mesenteric lymph nodes or in the other organs of the body, except those specifically mentioned.

The cultures made at the autopsy failed to yield a growth of Histoplasma capsulatum or any other fungus, in spite of the fact that the materials were taken and handled by one thoroughly conversant with the cultural characteristics of Histoplasma capsulatum.

After the facts just cited were known, the biopsy specimens were reexamined. Careful search with the oil immersion objective revealed Histoplasma capsulatum in each of the slides that had been previously examined. The organisms occurred, for the most part, 1 or 2 within a cell, instead of in the large numbers which we had seen previously, and it was necessary to search one section for an hour before the first organism was found. This experience has taught us that Histoplasma capsulatum may be exceedingly difficult to find even in well stained preparations. While in the vast majority of instances hematoxylin, in a hematoxylin and eosin stain, stains the organisms well enough so that they can be identified, on some occasions this method fails. In all instances it would appear to be desirable to search carefully sections stained with the Giemsa or the Masson trichrome method.

Case F (case 13, table).—A 12 year old boy, who lived in Ohio, suffered from what was considered to be aplastic anemia and was sick for eleven weeks before death. An autopsy was performed, and the essential abnormal condition noted was a generalized lymphadenopathy, especially of the mesenteric nodes. A slide prepared from one of these nodes was sent to the department of pathology in May 1936. A descriptive diagnosis of intracellular parasites was given at that time. After the diagnosis made in case A, this material was reexamined and the markedly hyperplastic reticuloendothelial cells of the lymph node were found to contain many organisms that were morphologically identical with Histoplasma capsulatum as it occurs in the tissues. The organisms had been seen but not identified in 1936.

Case G (case 49, table).—This case is reported here because of its unusual interest. It is published with the permission and approval of Dr. Paul Steiner and Dr. Paul Cannon, of the department of pathology of

Summary of Cases

Case	Author and Reference	Date	Locality	Race	Sex	Age	Lesions — Signs and Symptoms: Skin	Ear	Mouth-Nose Pharynx Larynx	Lymph Nodes	Lungs	Liver	Spleen	Gastro-Intestinal	Blood: Red Blood Cells mil.	Hemoglobin	White Blood Cells	Neutrophils %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %	Urine	Temp. °F	Duration	Method of Diagnosis: Blood Exam.	Bone Marrow	Biopsy	Autopsy	Culture	Distribution of Lesions: Autopsy or Biopsy: Centrifuged	Brain	Mouth-Nose	Larynx	Lungs	Lymph Nodes	Adrenals	Bone Marrow	Other Organs
1	Darling	1905	Panama	Negro	M	27							Large	Vomiting		60 %	2,200						97-101	3 -					+										Intestinal ulcers
2	Darling	1906	Panama	Negro	M	29					Pneumonia	2 fb	2 fb	Vomiting Diarrhea		70 %							Irreg. Fever				+		+	0	0	0	+	+	0	+		
3	Darling	1906	Panama	Chinese	M	55	+																97.5-102	5 m			+		+		0	0	+	+	+			Ulcers in ileum
4	Riehl	1922	Austria		M		+			Enlarged	Rales. X-ray	2 fb	3 fb		2.96-4.0	45-58 %	8,000-24,000					Alb. Casts		5 y				+	+									Verrucous endocarditis of tricuspid and aortic valves
5	Riley	1925	Minnesota	White	F	52					Pneumonia		Large	Large	Ascites	3.53	85 %	4,600	67	21	12		Alb. Casts	99-101					+	+	0	0	0	+	+	+			
6	Wade	1926	Philippine Islands				+																						+		+								Viscera
7	Phelps	1926	Honduras	Honduran	M	24						4 fb	Below Umbil.	Ascites		60 %							Alb.	98.6-101	3 m				+					+					
8	Crumarine	1928	California	Mulatto	M	42					Rales. X-ray	N.F.	N.F.	Diarrhea	2.9-3.1	70 %	3,600-4,500 12,000	80 85					Alb.	99-102.6	8 m				+	+	0	0	0	+	+	0			Ulcerative colitis
9	Muller	1931	Java	Javanese	M	7				Enlarged				Diarrhea Tumors										98.6-102.7					+							+			Spleen
10	Hansmann	1932	Iowa	White	M	43	+		M	Enlarged	Rales	Neg.	Neg.		4.2	82 %	10,200					Normal		16y				+	+	+	+		+	+	+	+			
11	Dodd	1932	Tennessee	White	M	6 mo		+			X-ray	Large	Large	Vomiting	2.07	6.4g	11,640 17,700	24	63	13			Alb. Casts	100	5 m	+			+	bl tl	+	0	0	+	+		+		Brain, ear, intestinal mucosa
12	Negroni	1934	Argentina					+																						+									
13	Weller	1936	Ohio	White	M	12				Enlarged														11 m					+					+					
14	Agress	1937	Missouri	White	M	7 mo			+		X-ray	2 fb	Large	Anal Fissure	3.1-4.4	66-74 %	5,850-6,700					Normal	98-102.4	7 m				+	+	0	+	0	+	+				Heart, colon
15	Balina	1937	Argentina	White	M	33	+			+ +	Enlarged	Rales	Neg.	Large	Diarrhea	4.3-3.39	70-80 %	10,500	66 65	6	16	2	Normal		10 y		+	+	+		+			+					Pharynx, trachea
16	Perrin	1937	Mexico																											+									
17	Stingily	1937	Mississippi	White	F	68			M		Normal													Norm.				+				M							Tongue
18	Wright	1938	Maryland	White	M	59					Cough	Neg.	Neg.		4.25	65 %	2,500	75	23	2			Normal	95-103	2 m			+	+	bl	+								
19	Shaffer	1938	Virginia	White	F	11 mo	+				Cervical		6 cm	Very Large	Vomiting Diarrhea	2.14	5.0-10.26 g	2,500-4,100	60 75	8	8		Normal	98.6-105	7 m				+	+	0	0	0	+	+	+			Pancreas
20	Williams	1938	Tennessee	White	M	56				Enlarged	Rales	1 fb	1 fb		3.82	11.6 g	12,100	29	71				Normal	102.4-103	2 y				+										Pharynx
21	R. Moore	1938	Missouri	White	M	54					Epitrochlear Inguinal	Cough Rales X-ray	Just Palp. Large	N.P. Large	Diarrhea	4.27	13.5 g	3,550-6,200	80	10	10		Alb. RBC Casts	104	7.5m				+	+									Vegetative endocarditis of aortic valve, Kidneys, pancreas, brain
22	Clemens	1938	Kentucky	Negro	F	33	+																																
23	W. Moore	1938	Missouri	Negro	M	33	+								4.41	13 g	3,500-9,000	88	12				Alb. Casts	98-107 101.4 104	7 m				+	bl	+	0	0	+	+	+			Prostate
24	Parsons	1938	Michigan	White	M	63				+	Enlarged	Rales	5 fb	2 fb	Neg.	4.11-4.93	70-80 %	3,400-5,900	57	24	16	3	Alb. Casts	102.8	11 m				+		0	0	M	0	0	+			Tongue, pharynx, colon
25	Amolsch	1938	Michigan	White	F	8 mo		+				X-ray	Large	Large		2.00-3.50	50-60 %	1,500-5,500	45 55	40 60	2 12			Fever	4 m	+		+	0										Spleen
26	Mantel	1938	Florida	White	M			+			Enlarged		Large	Large															+										
27	Rhodes	1939	Indiana	White	F	3 mo			+		Normal	Rales	Very Large	Very Large		2.72	7.1g	7,300-5,200	72	24	2-6		Alb.	100-104.8	1 m				+	bl	+	0	0	0	+	+	0		Kidneys, pancreas
28	Currie	1939	Indiana		M																								+									
29	Torrey	1939	Indiana	White	M	10				Enlarged				Large															+	+	bl				+				Ileum, colon
30	Humphrey	1939	Michigan	White	M	17	+	+	M		Cervical axillary	Pneumonia	Palp.	N.P.		1.6-5.0	40-105 %	1,500-4,500	29 60	4			Normal	98.6-103	18 m				+					+	+				Heart, kidneys, pancreas
31	Humphrey	1939	Michigan	White	M	46						X-ray	Palp.	Large	Vomiting	3.38-4.36	58-78 %	6,200	47 72	43 24	3 4		Normal	98.6-105	7 m				+					+	+				Kidneys
32	Reid	1939	Virginia	Negro	M	38				+	Enlarged	Rales	N.F.	N.F.	Diarrhea	2.50	54 %	3,200	56	26	6	4	Alb. Casts	100-103	4.5m	+	+	+	+	+	bl				+	+		+	Pancreas, kidneys, ileum, colon
33	Gunter	1939	Alabama	White	F	54					Normal		N.P.	4 fb	Rectal Hemorrhage	4.00	60 %	4,000	60	38		2		100-103	4 m				+					+	+				
34	Meleney	1939	Tennessee	White	M	69						Pneumonia				3.80	9.5g	12,800	91					99.4-102	3 m				+		+	0	0	0	+	0	0		
35	Meleney	1939	Tennessee	White	M	50						Tuberculosis	N.P	N.P.	Diarrhea	4.00	12.2 g	13,600	65				Alb. Cells	Norm.	2 m				+					+					
36	Villela	1939	Brazil	Mulatto	M	3	+						Large		Diarrhea										2 m				+									Liver
37	Parsons	1939	Michigan	White	F	25	+	0	+		Normal	Neg.	Palp.	N.P.	Rectal Hemorrhage	1.10-4.10	20-63 %	2,200-5,600	69	27	4		Normal	97.8-102.6	15 m	0	0	+	0	+			M						
38	Almeida	1939	Brazil					+																					+									
39	Almeida	1939	Brazil																																				
40	Martin	1939	California	White	M																																		
41	Gray	1939	Missouri																																				

39	Almeida	1939	Brazil									Sputum																									
40	Martin	1939	California	White	M																																	
41	Gray	1939	Missouri	White	M	Boy					Cervical																											
42	Anderson	1940	Tennessee	White	F	6 mo	+	+			Cervical	X-ray	Large	Large	Diarrhea	1.8-3.8		1,850-2,500		62-80					99.4-104	4 m	0		+		+		+	+		Thymus, kidneys
43	Henderson	1940	Missouri	White	M	70							5 fb	N.P.	Diarrhea	3.69		11,400	66	12				Alb. Cells	97-102.4 Fever	2 m			+		+			0	+	+	Kidneys, intestine
44	Brown	1940	Texas	White	M	48			+	+	Normal	Neg.	N.P.	N.P.	Ulcers	4.96	11.9	6,600	68	27	4	1				25 m			+	+	+		+	+	+	+	Liver, intestine
45	Derry	1940	England	White	M	30					Enlarged	Dy. ...ea	Large	Large		4.40	6.5	13,000-16,000	76	13	9			RBC Casts	100-101	6 m	0	+	+				0	+			
46	Ramsey	1940	Michigan	White	F	63						X-ray	N.P.	N.P.	Occult Blood	3.40	8.5	2,000	60	40				Alb. RBC	102-106				+		+			+	0	+	Kidneys
47	Parsons	1940	Michigan	White	M	41					Enlarged	X-ray	7 cm	3 cm		4.0-5.0	7.5	9,550	76	16	7	1		Alb. RBC	97-104	21 m	+		+		+		+	+	+	+	Stomach, ileum, appendix
48	Scott	1940	Kentucky	Negro	M	15 mo					Enlarged	X-ray	3 fb	2 fb	Neg.	2.40-1.86	7.2	4,100-2,900	60	12	6			Alb. Casts	98.6-104	3 m			+		+			+	+		Ileum
49	Steiner	1940	Illinois	White	M	56	+				Enlarged		2 cm	6 fb		4.40-3.20	7.8-9.2	11,300-1,400	66-76	31-23	12-2	7-5	1	Alb.	103				+		+			+	+		
50	Palmer	1940	Michigan	White	M	45	+		M	+	Normal	Cough	N.P.	Large			10-6g	4,000-1,650	70	23	2	5	1	Alb. RBC	100-101	7 m	0	0	+	+	+	+	+	+	0	0	+	
51	Poncher	1940	Illinois	White	F	44 mo						Normal	Large	5 fb	Diarrhea	2.60	7.8	9,400	49	42		5	1	Alb.	102	2½ m			+		+			+	+	+	Thymus
52	VanPernis	1940	Illinois	White	M	63	+	M	+	+		Relea	3 fb	Large		5.12	10.4-10.2	7,950-5,820						Neg.	93-99.6	23 m	0	0	+		+		+				
53	Parsons	1940	Michigan	White	M	49	+	+	M	+	Enlarged	Normal	2 fb	2 fb		4.4-5.0	8.7-8.5	9,650-9,750	70	16	9	5		Casts	99.4-101.5	10 m	0	+	+	+	+	+	+	+	+	+	+	Pharynx, parathyroid, kidneys, intestinal ulcers
54	Hild	1941	Texas	White	F	5 mo		+			Submax. Inguinal Cervical Inguinal	Pneumonia	3 fb	3 fb		4.85	8.4	7,750-1,500	44	52	1					102-103	1 m	0	+		+	bl	+	0		+	+	+	Thymus, kidneys, intestinal ulcers
55	Dawson	1941	Tennessee	White	F	6 mo							Large	Large		3.0-4.0	8-12g	7,000-1,000								1 m	0	+		+	+			+		+	Thymus
56	Allen	1941	Missouri	White	M	71			M																					+	0	+		K				Tongue
57	Simson	1941	Rhodesia	White	M	55	0		M	+	Cervical		4 in	4 in		4.96	96	2,700	65	18	12	4	1		98.4				+		+		M	+				Tongue
58	Key	1941	Missouri	White	M	47						X-ray	N.P.	N.P.		4.8-3.63		12,650-18,600	85	11	3		1	Normal	99.5-101.5	8 m			+	0								Knee and femur
59	Jorstad	1941	Missouri	White	M	60			M																					+				M				Tongue
60	Manchester	1941	Washington D.C.	White	M	63							Large	Large	Complaints															+						0	+	
61	Hunter	1941	Washington D.C.																											+								
62	Dean	1942	Missouri	White	M	41	+			+															99.8	9 m			+	0		+		+				Trachea
63	Brodere	1942	Oklahoma	White	M	47			+				Palp.			4.16	11.2	6,900						Alb.	103	9 m			+	+	+							Vegetative endocarditis of mitral and aortic valves
64	Bowser	1942	Illinois	White	M	11 mo	+		N				Palp.	Palp.	Anorexia	3.6	3.7g	10,000	67	10	3				103.3	11 m			+	bl	+			+	+	+	+	Pancreas, appendix, cecum, colon
65	Byrne	1942	Louisiana	White	M	55			M	+	+	Cervical Submental Normal	N.P.	N.P.										Alb.		2 m			+		+	+	M	+				
66	Dawson	1942	Tennessee	White	M	3 mo			M				Large	Large	Vomiting	1.50	4.2g	2,000-4,000										+		+	+	+						
67	Colvin	1942	Alabama	Negro	M	23						Axillary	X-ray	2 fb	4 fb	3.10	60	5,000	75	23	2			Alb.	104	2 m			+		+			+	+	+	
68	R. Moore	1943	Missouri	White	F	4					Enlarged	Pneumonia	X-ray	3 cm	4 cm	Anorexia	2.76	9.3g	1,800-6,000	66	12	2			Alb. YBC	104	5 w			+	bl	+			+	+	+	
69	Burden	1943	New York	White	M	68				M	+		Palp.	Palp.	Anorexia	3.42-4.11	68-81 g	9,600-5,400	53	33	2	5	1	Alb. Casts	102				+	+	+		M		+	+	
70	Thomas	1943	North Carolina	White	M	44	0	0	0	0	0	General	X-ray	3 cm	4 cm	Hiccuping	2.87-6.33	13.5-10g	3,000-9,000	48	44	8			Alb. Casts	100-105	4 y			+	+	0	+		+	+	+	Kidneys
71	Parsons	1943	Michigan	White	M	60			M	+	+	Cervical	X-ray	Palp.	N.P.	Anorexia	3.8-4.0	73-76g	5,600-7,000	74	14	10	1	1	Alb.	98-105	3 m	0	0	+	+	0	0	0	M	0	+	0	0	+	Vegetative endocarditis of tricuspid valve

+ = Lesions found or diagnostic procedure successful
0 = No involvement of organ or examination unsuccessful

Under "Mouth - Nose":
M = Mouth lesion
N = Nose lesion
+ = Mouth and Nose involved

fb = Fingersbreadth below costal margin
cm = Centimeters below costal margin
in = Inches below costal margin
Palp. = Palpable
N.P. = Not palpable

bl = Blood culture successful
ti = Culture of tissues successful

m or mo = Months
y = Years
w = Weeks
g = Grams

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the University of Chicago. Dr. Steiner provided us with the data. The patient was a white Illinois farmer 56 years of age. He became ill in October 1939. There were abdominal pain, vomiting, anorexia, loss of weight, dyspnea, a mass in the abdomen and lymphadenopathy. By biopsy of an inguinal lymph node in January 1940, Hodgkin's disease was diagnosed, and the nodes responded well to roentgen therapy. Later there was a papular eruption of the skin which was thought due to Hodgkin's disease. All the peripheral lymph nodes were enlarged, discrete and nontender. Some were as large as a golfball. Roentgenographs of the thorax showed widening of the mediastinal shadow. The liver could not be felt until terminally, when it was palpable 2 cm. below the costal margin. The spleen was always palpable 4 to 8 fingerbreadths below the costal margin. There was no fever early in the illness, but later there was irregular elevation of temperature up to 103 F. Toward the end, the pulse rate was 120 and the blood pressure was 110 systolic and 76 diastolic. Laboratory findings included: red blood cells, 4,400,000 to 3,200,000; hemoglobin, 78, 56 and 70 per cent in successive determinations; white blood cells, 11,300 to 1,400 (terminal), with differential counts of 56 to 62 per cent neutrophils, 23 to 31 per cent lymphocytes, 2 to 10 per cent mononuclear cells, 5 to 7 per cent eosinophils and 1 per cent basophils. Later the number of monocytes went up to 12 per cent. The urine showed albumin on one occasion, and a positive reaction to a benzidine test was obtained from the stool on one occasion.

The autopsy was done by Dr. Steiner on Sept. 13, 1940. It showed the typical lesions of Hodgkin's disease involving the abdominal lymph nodes, spleen, liver and bone marrow. Microscopic examination also revealed the lesions of histoplasmosis in peripheral and visceral lymph nodes, lungs, liver, spleen and bone marrow. The kidneys and adrenals showed no organisms. Bone marrow from eight different bones was examined, and it was extensively replaced by small areas of necrosis which were surrounded by large mononuclear phagocytes. These contained great numbers of organisms which were morphologically identical with Histoplasma capsulatum. In the bone marrow the lesions of Hodgkin's disease were sometimes separate and sometimes intermixed with the much more extensive lesions of histoplasmosis. It was Dr. Steiner's opinion that the leukopenia was caused by the replacement of the marrow by the latter lesions. It is agreed by the pathologists who have seen the sections from this case that both Hodgkin's disease and histoplasmosis were present. The history of the case suggests that Hodgkin's disease came first, but of course this cannot be proved. The question must be asked: Did Hodgkin's disease, a disease in which cells of the reticuloendothelial system become malignant, predispose this man to histoplasmosis, a disease which is characterized by the parasitization of the cells of the reticuloendothelial system by the yeastlike form of the fungus Histoplasma capsulatum?

The following are brief notes on a few additional cases which have come to our attention but which have not appeared in the literature as yet.

Case H (case 17, table).—A 68 year old white woman, a patient of Dr. Karl O. Stingily, Meridian, Miss., who had always lived in Mississippi, was first seen in 1937 with an ulcer on the tongue. Biopsy of the ulcer led to the diagnosis of carcinoma, grade I. The lesion was treated with radium and healed. One year later two ulcers appeared, and another biopsy showed extensive infiltration of the base of the ulcer with large mononuclear phagocytes which were heavily parasitized with organisms morphologically the same as Histoplasma capsulatum. One of us (R. J. P.) has had the privilege of examining the second specimen from this case and of confirming the diagnosis. After this second biopsy, the lesions were treated with "superficial" roentgen irradiation and healed. At the time of writing, after the lapse of five years, the patient is in good health and shows no manifestations of the disease.

The husband of this patient also had a chronic punched-out ulcer on his tongue. This ulcer antedated the one in case H by several months, according to Dr. Stingily. This of course suggests direct contact infection. It was not possible to obtain a specimen for biopsy, and the patient died in 1941. Since autopsy was not allowed, proof of the causation of the ulcer is lacking.

Case I (case 60, table).—A 63 year old white man, a patient of Dr. Benjamin Manchester, Washington, D. C., had splenomegaly and hepatomegaly. Toward the end of his illness, in 1941, he showed evidence of adrenal insufficiency. He died in spite of treatment with adrenal extract. At autopsy there was bilateral adrenal necrosis due to histoplasmosis. Organisms could not be found in any other organ of the body. The diagnosis of histoplasmosis was confirmed by Colonel Ash, of the Army Medical Museum.

Case J (case 65, table).—The information on this case was sent to us by Dr. Edward L. Burns, of the Louisiana State University School of Medicine. A 55 year old white man, a native of Louisiana, entered the hospital complaining of hoarseness following a "chest cold." There was dysphagia, and ulcers appeared at the angles of the mouth and on the hard palate. The aryepiglottic folds were thickened. The submental and cervical lymph nodes were enlarged, but the liver and spleen were not enlarged. The blood counts were within normal limits. The urine showed a trace of albumin. The patient died in October 1942. At autopsy disseminated histoplasmosis was found. One of us (R. J. P.) chanced to see a section from the larynx in April 1943.

REVIEW OF THE PRESENT STATUS OF HISTOPLASMOSIS

A study of the literature of histoplasmosis has been made, and a brief summary of the clinical data and autopsy observations for each case, when such are available, is given in the accompanying table. The table includes 6 cases which have been observed at the University of Michigan, 5 of which have previously been mentioned in the literature [19] but not described in detail. Also included are the available data on 15 cases which have not yet appeared in the literature. Several of these cases will undoubtedly be published, and we are indebted to the physicians concerned with them for the information that they have made available at this time.

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INCIDENCE AND DISTRIBUTION OF HISTOPLASMOSIS

For the purpose of giving as accurate an idea as possible of the frequency of histoplasmosis, or at least the frequency of recognition of the disease, the cases in the table have been arranged, as nearly as possible, in the order of their occurrence rather than in their order of publication. In some instances it has been impossible to establish this order accurately, and in these instances we have made as close an approximation as possible.

It will be noted that since 1936 the number of cases of the disease appears to have increased suddenly, so that 15 cases were discovered in 1939 and 12 cases in 1940. Since the distribution of the disease appears to have been worldwide (see following section) over the past three decades, one is tempted to think that the reason for the apparently increased incidence lies in better recognition rather than in a truly increased frequency of occurrence. Indeed, 3 of the cases (4, 13 and 21) were properly identified from two to eighteen years after the patient's death. However, if one is to believe that the increase in number of cases is due only to better recognition, it is remarkable that many more cases have not been identified from the literature and from older cases in many laboratories. Search through large numbers of reports of the older complete autopsies at the University Hospital has failed to reveal a single case of histoplasmosis. During the fall of 1938 and the spring of 1939 a total of 4 cases of histoplasmosis was found in Southern Michigan by three pathologists. Each of these pathologists recognized the disease as something new to him, and each arrived independently at the proper diagnosis. Five other cases occurred in Michigan during the next two years, and still another patient died of the disease in July 1943. Similarly, the first case to be found in Nashville, Tenn., was diagnosed in 1932. No more cases were encountered there until 1937, and from 1937 through 1942 one or more cases have occurred each year. It seems most probable that the incidence of the disease is definitely on the increase.

Distribution.—Geographic Incidence: The disease is widespread throughout the world. In the various countries, cases have occurred as follows: Austria, British Honduras, East Java, England, Mexico, the Philippines and Southern Rhodesia, 1 case each; Argentina, 2 cases; Brazil and the Panama Canal Zone, 3 cases each, and the United States, 56 cases. The cases in the United States have been distributed as follows: Florida, Iowa, Louisiana, Maryland, Minnesota, Mississippi, New York, North Carolina, Ohio and Oklahoma, 1 case each; Alabama, California, Kentucky, Texas, Virginia and Washington, D. C., 2 cases each; Indiana, 3 cases; Illinois, 4 cases; Tennessee, 7 cases, and Missouri and Michigan, 10 cases each. It can be seen that more than a third of the cases have occurred in four Midwestern States.

Instead of histoplasmosis being a disease with a tropical distribution as suggested by Darling [1c] it is now apparent that it must be looked for in the temperate and subtropical regions of the world as well.

Race: The race to which each patient with histoplasmosis belonged is given in column 5 of the table. Data are available in 63 cases. The disease has been seen in 51 white persons, 7 Negroes, 2 mulattoes, 1 Javanese, 1 Chinese and 1 Honduranean.

Sex: Histoplasmosis occurs more frequently in males than in females, as demonstrated by the data in the table. In the 65 cases in which data are available, 51 patients were male and 14 were female. If these figures are broken down further, it is found that up to and including the age of 10 years the incidence is the same in the two sexes, there being 8 patients of each. Of the 49 patients older than 10 years of age, 43 were males and 6 were females.

Age: Every age group is susceptible to infection with Histoplasma capsulatum. The table gives the ages of 60 patients in the present series of cases. They are distributed as follows: 0 to 1 year, 11; 1 to 9 years, 4; 10 to 19 years, 3; 20 to 29 years, 5; 30 to 39 years, 5; 40 to 49 years, 11; 50 to 59 years, 10; 60 to 69 years, 9, and 70 to 79 years, 2. The incidence is highest during the first year and then falls off sharply but reaches another peak during the fifth, sixth and seventh decades. The first symptoms of the disease were noted during the second month of life in 3 cases (27, 51 and 66) and possibly during the first month of life in case 64. The oldest patient reported so far is the one in case 56. This patient died at the age of 71 years.

Occupation: The occupations of 30 of the patients in this series who were more than 12 years of age are known. Ten of the 30 were farmers, 4 were laborers, 2 were bartenders and 2 were waiters. There was 1 each of the following types of worker: baker, carpenter, janitor, lawyer, mine manager, printer, salesman, school teacher, soldier, steel worker, student and teamster.

SIGNS AND SYMPTOMS OF HISTOPLASMOSIS

Infection with Histoplasma capsulatum is manifested in many different ways. There may

be ulcerative lesions of the skin and/or mucous membranes of the mouth and pharynx. There may be localized or generalized lymphadenopathy. Most of the viscera may be involved (all have been involved in one case or another), or only one organ, such as the adrenal, may be affected. The intestinal tract is frequently the site of ulcerated lesions.

Skin.—Of the 61 cases on which there were sufficient data for analysis, in 19 some form of skin lesions were present: ulcers in 9 instances, a papular eruption in 4 (cases 4, 10, 15 and 59), and purpura, usually occurring in the last two or three days of life, in 6. Petechial hemorrhages and bullous lesions were each noted once. Chronic ulcers sometimes occur in the center of the papular lesions. The ulcers are frequently deep, with sharp, steep edges, giving a punched-out appearance. They are well illustrated in the paper of Baliña and associates.[20] The papular eruption is illustrated in the paper of Hansmann and Schenken.[9]

Ear.—The middle ear or the aural canal was the site of lesions in 8 instances. True otitis media was described in 5 of these (cases 11, 25, 42, 52 and 54). In case 11 the organisms were demonstrated in the pus from the middle ear. In case 30 the patient had been treated for a fungous infection of his ear shortly before the onset of generalized symptoms of histoplasmosis.

Eye.—Reid and associates,[21] in case 32, described "small, white irregular areas surrounded by hemorrhage in the ocular fundi. They were not unlike tubercles." Definitive changes in the eyegrounds have not been noted in other cases.

Mouth and Nose.—Ulceration of the mucous membrane of the mouth, most frequently of the tongue, was noted in 14 cases. In 4 additional cases there was ulceration of the mucous membrane of the nose as well as of the mouth. In case 64 the patient had ulcerations in the nose but none in the mouth. Perforation of the nasal septum was noted in 3 cases. In cases 14 and 37 the perforation was produced by infection with Histoplasma capsulatum. In case 24, the perforation appeared to be well healed and may have had no relation to histoplasmosis. In at least 4 cases (cases 17, 53, 56 and 59) the clinical diagnosis on lesions of the oral mucosa was carcinoma.

Pharynx.—Granulomatous and ulcerated lesions were found in the pharynx in 10 instances. The lymphoid tissue in the tonsils and in the mucosa of the pharynx is most frequently the site of the lesions.

Larynx.—Granulomatous and ulcerative lesions appeared in the larynx in 10 instances, usually in association with lesions of the pharynx. Aphonia, dysphonia and dysphagia were frequently present with these lesions.

Lymph Nodes.—The superficial lymph nodes were enlarged in 29 of the 61 cases that can be analyzed. The enlargement was generalized in 16 instances. The cervical nodes were involved alone in 5 cases and along with another group of regional nodes in 4 additional instances. In 1 instance (case 22) the inguinal nodes alone were enlarged. When the lymph nodes were enlarged, they frequently reached a diameter of 1 to 2 cm. or more. They were moderately firm and frequently were freely movable but occasionally were matted together. The nodes were sometimes tender. There was roentgenographic evidence of enlargement of the mediastinal lymph nodes in 4 instances.

Lungs.—The findings in the lungs in cases of histoplasmosis are variable, depending on the degree and the type of involvement. In this series, cough was noted as a symptom in 11 cases. Rales of various sorts were mentioned in 13 cases. A friction rub was noted 4 times, and a diagnosis of pneumonia was made at least 8 times. In 11 instances, a diagnosis of tuberculosis had been made or at least seriously entertained before death. The clinical evidence for tuberculosis in these cases had been apical opacities and cavities seen roentgenographically, miliary lesions scattered throughout the lungs, or tubercle bacilli in the sputum. Tubercle bacilli were found in the sputum in 3 instances (cases 24, 35 and 70), while in a fourth (case 34), tubercle bacilli were found in pulmonary lesions at autopsy. Miliary lesions have been found in the lungs on several occasions (cases 24, 34, 35, 53, 67, 69, 70 and 71). No tubercle bacilli could be found in the miliary lesions in case 24 in spite of the presence of pulmonary tuberculosis. In case 53, a single Histoplasma capsulatum organism was found in one of the miliary lesions. No tubercle bacilli were found, but this was to be expected, since no active tuberculous focus was present. In 5 instances (cases 4, 15, 24, 35 and 70) roentgen examination revealed parenchymal changes which were considered typical of active pulmonary tuberculosis. In cases 4 and 15 there was no mention of tuberculosis at autopsy, while in the other cases typical

20. Baliña, P. L.; Negroni, P.; Bosq, P., and Herrara, J. A.: Histoplasmosis de Darling. Primer caso sudamericano, Rev. argent. dermatosif. **25**:491, 1941.

21. Reid, J. D.; Scherer, J. H.; Herbut, P. A., and Irving, H.: Systemic Histoplasmosis Diagnosed Before Death and Produced Experimentally in Guinea Pigs, J. Lab. & Clin. Med. **27**:419 (Jan.) 1942.

active tuberculous lesions were found along with the lesions of histoplasmosis. Since the signs and symptoms of pulmonary histoplasmosis have frequently been mistaken for those of pulmonary tuberculosis, and especially since the two conditions may exist together, the differential diagnosis will be difficult. The intradermal test for Histoplasma capsulatum infection [22] should help in this regard.

Liver.—The liver is frequently enlarged. It was palpable in 39 of the 61 cases. It was not palpable in 12 instances, and in the remainder of the cases the status of the liver was not mentioned. In patients less than 1 year of age the liver has invariably been enlarged. In most instances its edge has been 2 to 3 fingerbreadths below the costal margin, but it may extend 7 fingerbreadths below the costal margin. The surface is usually firm and smooth to palpation, while the edge is frequently slightly rounded. Jaundice was present in cases 11 and 36. Ascites has occurred a few times.

Spleen.—The spleen was palpable in 37 instances, not palpable in 14 cases and not mentioned in the remainder. It was palpable in all patients under the age of 1 year. It may be sufficiently enlarged to be felt below the level of the umbilicus, but the enlargement was more commonly measured in a few fingerbreadths. The surface usually felt moderately firm and was smooth. In all but 11 cases, when either the spleen or the liver was palpable the other organ was also palpable.

Gastrointestinal Tract.—The symptoms relating to this tract are many and varied. Diarrhea was present in 12 cases, and in case 43 the symptom complex was indicative of an ulcerative enteritis. Vomiting was present in 6 of the cases. Hemorrhage per rectum occurred in cases 33 and 37. In 1 of these (case 37) it was massive and recurrent, but since an autopsy was not done the exact relationship of the hemorrhages to histoplasmosis is not known. Anorexia has been present in most of the cases, and loss of weight or true emaciation was almost always present.

Heart.—On the basis of heart murmurs and irregular fever, subacute bacterial endocarditis was diagnosed in case 63. A vegetative endocarditis caused by Histoplasma capsulatum was found at autopsy.

22. (*a*) Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, J. A. M. A. **117**:436 (Aug. 9) 1941. (*b*) Zarafonetis and Lindberg.[18]

Blood Pressure.—A great majority of the patients showed no abnormality of the blood pressure. However in 3 cases a striking hypotension has been recorded (case 43, 80 systolic and 65 diastolic; case 50, 95 systolic and 55 diastolic; case 53, 88 systolic and 62 diastolic). At autopsy it was found that in each of these cases there was extensive caseation necrosis of the adrenals. Caseation necrosis was found in several other cases, as will be mentioned later, but the blood pressures recorded for these were not abnormally low.

Red Blood Cell Count.—The red blood cell count was recorded in 38 cases. For the purpose of condensation of the data we have taken the average figure or the only figure that is given as a basis for the following statements: In only 2 cases was the count greater than 5,000,000. In 15 cases the count was between 4,000,000 and 5,000,000, in 19 cases between 3,000,000 and 4,000,000 and in 9 cases between 2,000,000 and 3,000,000; in 1 case the only count recorded was 1,500,000. It is evident that a moderate anemia is the rule in this disease and a severe anemia occurs fairly frequently.

Hemoglobin.—The hemoglobin is reduced in proportion to the reduction in the number of red blood cells. In each case in which the blood was completely studied, the anemia was described as a hypochromic anemia, either of microcytic or of normocytic type.

White Blood Cell Count.—In the table we have recorded the only count or the highest and the lowest count when more than one count was available. The total white cell count was recorded in 48 of the 71 cases. A count in the normal range, of 5,000 to 10,000, was recorded in 23 cases, but in 11 of these at least 1 other count was less than 5,000, and in 1 case above 10,000. Counts of 5,000 or less were recorded in 28 cases, and in 18 of these cases the counts were consistently below 5,000. Counts of over 10,000 were recorded in 15 cases, and in at least 2 of these cases (cases 4 and 20), histoplasmosis was associated with leukemia. In 1 of the 15 there was an accompanying count that fell into the leukopenic range, and in another case, a count that fell into the normal range. Restating these figures in another way, counts consistently in the leukopenic range were recorded in 18 cases, consistently in the normal range in 11 cases and consistently above 10,000 in 9 cases (disregarding the 2 cases of leukemia).

Differential White Blood Cell Count.—This shows no consistent changes and is subject to wide variations. The neutrophilic granulocytes

ranged from 9.8 to 91 per cent, with 45 to 80 per cent most frequent. The lymphocytes ranged from 8 to 80 per cent, the common range being 20 to 60 per cent. The monocytes ranged from 0 to 16 per cent (from 1 to 4 per cent in most cases). In a few instances there was a considerable increase in the percentage of monocytes during the last few days or weeks before death. The percentage of eosinophilic granulocytes ranged from 0 to 32 per cent, 0 to 1 per cent being usual. From 0 to 1.1 per cent of basophilic granulocytes have been seen, but in the majority of instances no basophils were recorded.

Blood Smears.—As has been pointed out, histoplasmosis was first diagnosed in life (case 11) by finding the yeastlike form of the fungus in the circulating monocytes. Since then blood smears have been studied intensively in known cases of the disease, but the organisms have been found in the monocytes in only 2 other cases (cases 25 and 32), and then only late in the course of the infection. In case 32 there was parasitization of both monocytes and neutrophils. In 1 of our cases (case 47), numerous Histoplasma capsulatum organisms were present in the cytoplasm of the neutrophilic granulocytes (fig. 4) in smears taken on the last two days of life. Careful examination of daily smears taken earlier revealed no organisms, and at no time were organisms found in monocytes. The results of examination of blood smears for Histoplasma capsulatum can be considered diagnostically significant only when the organisms are found, and both the polymorphonuclear cells and the monocytes must be searched for them.

Temperature.—The temperature is irregularly elevated to a variable degree in most cases of histoplasmosis. Most commonly it reaches 100 to 102 F. at some time during the day, but temperatures as high as 107 F. have been recorded. In only 2 instances in this series was the temperature reported as normal. Chills occurred in some cases, and in case 67 they recurred nightly. Night sweats were mentioned among the symptoms in some cases (cases 32 and 53).

Blood Proteins.—Determinations of the blood proteins have been recorded in only 7 cases of histoplasmosis, but in each of these a definite abnormality has been demonstrated. In 4 of the cases reviewed the total protein content was normal but there was a reversal of the albumin-globulin ratio. In case 21, the albumin ranged from 2.6 to 3.1 and the globulin from 4.6 to 5.2 Gm. per hundred cubic centimeters. The albumin was 2.9 and the globulin was 3.7 Gm. per hundred cubic centimeters in case 24. In case 53 the albumin was 3.9 and the globulin 4.3 Gm. In case 70 there was an albumin content of 2.5 Gm. and a globulin content of 4.3 Gm. In the 3 others (cases 11, 32 and 51), a reduction of the total protein to 4.3, 4.7 and 4.4 Gm., respectively, was noted. Edema was described in case 11. Albumin was present in the urine in each of the cases in which there was a disturbance of the blood proteins.

Urine.—Examination of the data on the collected cases does not reveal any specific changes in the urine. Albumin was present in 24 of the cases in which the urine was mentioned. Casts, red blood cells and white blood cells were also present in a smaller number of cases. It seems possible that Histoplasma capsulatum might be cultured from the urine of patients in some instances. It has been cultured from the urine of guinea pigs that had been infected by intravenous injection of the fungus by Reid and coworkers.[21]

Duration of the Disease.—Infection with Histoplasma capsulatum, as far as we know now, is almost universally fatal, death occurring a few weeks or months and rarely some years after the infection. In the great majority of instances the infection lasted less than one year. For the 39 cases in this category, death occurred an average of five months after the onset of illness. In another group of 6 cases, symptoms lasted from one to two years, with an average of twenty-one months. In a third group there were 4 cases which lasted four, eight, ten and sixteen years. In case 5 the patient may have had histoplasmosis for many years but the history is indefinite. The third group contains the 3 cases in which Histoplasma capsulatum has produced long-standing chronic papular and ulcerative lesions of the skin. The average duration of symptoms in the 10 infants less than 1 year of age was five and one-tenth months, approximately the same as for the larger group of 39 patients which included these infants. Four patients (cases 17, 26, 57 and 59) are still living six, five, two and two years after the diagnosis was established. Three of these (cases 17, 57 and 59) have had ulcerative lesions on the tongue as the only presenting sign of histoplasmosis.

METHODS OF DIAGNOSIS

Blood Smears.—It has already been mentioned that the yeastlike form of Histoplasma capsulatum parasitizes the monocytes and the polymorphonuclear cells of the circulating blood. Examination of blood smears is the simplest and most readily available diagnostic procedure that

can be used. However, since in this large group of cases the organisms were found by examination of the blood cells in only 4 instances, it is obvious that the method should be relied on only when the organisms are found.

Sternal Bone Marrow.—The sternal bone marrow has been studied by sternal puncture in at least 9 cases, the organism being found in 5 of these. Three of the cases in which this method of diagnosis was successful were cases of histoplasmosis in infants. In case 54 Histoplasma capsulatum was successfully cultured from material obtained by sternal puncture.

Biopsy.—In 29 of the cases in this series, it has been possible to establish a diagnosis by histologic examination of biopsy material. In 3 of these cases the material for biopsy was obtained by a sternal puncture. In 2 cases sternal marrow and other biopsies were both diagnostic. In some instances (e. g. cases 37 and 53), the diagnosis was confirmed by culture of some of the material obtained for biopsy. Up to the present time, biopsy appears to be the most successful method of detecting this disease.

Cultures.—The only means for establishing a positive diagnosis of histoplasmosis at the present time is to obtain a culture of the organism and identify it by means of its definitive characteristics in the mycelial form. The mycelial form develops on nearly all of the ordinary bacterial and fungous mediums when they are kept at room temperatures. On fungous mediums, such as Sabouraud's, the mycelial form will develop at incubator temperatures, but growth is less rapid than at room temperatures. The yeastlike form, as obtained directly from the tissues or the blood, can be grown at 37 C. on blood agar and other neutral or slightly basic mediums which have a high content of protein. The tubes may or may not be sealed. The organism grows slowly and may therefore be difficult to isolate from contaminants. The cultures should be kept for at least two and better for three weeks before they are discarded as negative.

At present there appears to be only one species, Histoplasma capsulatum, of the genus Histoplasma. The most recent and the best discussion of the classification of this fungus was published in 1941 by Conant.[13]

Cultures of Histoplasma capsulatum have been obtained in 23 of the cases in this series. This number would undoubtedly have been much higher if the culture mediums in other cases had not been discarded after a lapse of only four or five days. In 18 instances Histoplasma capsulatum was grown from the tissue obtained for biopsy or at autopsy. In 9 instances the organism was grown in cultures of the blood, and in 1 instance it was grown from a culture of sternal marrow. In case 39 it was cultured from sputum. In several of the cases it was obtained from more than one source.

Cutaneous Test.—Another method of diagnosis which holds some promise of being useful is a cutaneous test. The intradermal injection of a filtrate obtained from the liquid medium in which the fungus has grown results in the production of erythema and a wheal at the site of injection in infected persons. Such a test was developed and used successfully in a patient having histoplasmosis by Van Pernis, Benson and Hollinger.[22a] The same sort of test was developed by Zarafonetis and Lindberg,[18] and it was found to give excellent reactions in rabbits infected with Histoplasma capsulatum. The antigen used in case 71 yielded negative results. This antigen was ten months old and may have been inactive.

Inoculation of Animals.—Many laboratory animals have been found susceptible to infection with Histoplasma capsulatum, among them mice,[23] guinea pigs,[23a] rats,[9] rabbits,[24] dogs,[25] monkeys [8] and chick embryos.[26] It seems probable that in some instances in which it is impossible to obtain uncontaminated material for culture, the subcutaneous, intraperitoneal or intravenous injection of ground biopsy material into one or more of these animals might render the isolation of Histoplasma capsulatum simpler than the use of culture mediums alone. In case 53 lymph nodes were removed for culture and isolation of the organism on two separate occasions. We succeeded in obtaining the organism in culture each time, but we also successfully inoculated young mice with suspensions of the nodes. The mice were inoculated intravenously, and all became infected with the organism.[12] Injection of biopsy material from case 71 into guinea pigs failed to induce an infection. Intraperitoneal injections into mice are known to be satisfactory.[23a]

TREATMENT

Many types of treatment for histoplasmosis have been tried during the last ten years. Some have met with questionable success, but most

23. De Monbreun.[8] Parsons.[12] Tager and Liebow.[13]

23a. Negroni.[14a] Redaelli and Ciferri.[14b] Reid and others.[21]

24. Redaelli and Ciferri.[14b] Zarafonetis and Lindberg.[18] Van Pernis and others.[22a]

25. De Monbreun.[8] De Monbreun, W. A.: The Dog as a Natural Host of Histoplasma Capsulatum: Case of Histoplasmosis in This Animal, Am. J. Trop. Med. **19**:565 (Nov.) 1939.

26. Moore, M.: Histoplasma Capsulatum: Its Cultivation on the Chorioallantoic Membrane of the Developing Chick and Resultant Lesions, Am. J. Trop. Med. **21**:627 (Sept.) 1941.

have not appeared to alter the course of the disease. In case 26, biopsy of a lymph node resulted in a diagnosis of leishmaniasis. On the basis of this diagnosis, neostam,[27] an antimony preparation, was given with resulting clinical recovery. Meanwhile sections of the lymph node were reexamined and the proper diagnosis of histoplasmosis was made. At the time of the last report,[28] October 1942, this patient was in good health and working every day, four years after his treatment. On the basis of this result we gave neostam (stibamine glucoside) in case 53. Because of the toxic effect of the drug it had to be discontinued when only 0.56 Gm. had been administered. At about the same time neostam was given in case 50, but it was soon refused by the patient. In case 57 the patient has shown striking improvement following treatment, first with an antimony preparation and then with antimony alternated with one of the new diamidine preparations.[29] This patient is still alive. The patient in case 69 was treated much as was the one in case 57. The diamidine preparation was stilbamidine[29a] (4, 4-diamidinostilbene), and the antimony was in the form of neostibosan.[30] Treatment was unsuccessful.

Case 50 is of special interest. As mentioned in the preceding paragraph, an antimony preparation was used first. Only a small amount of the substance was administered. The patient was then given 4 Gm. of sulfathiazole per day. He continued to feel worse; hence this was discontinued after ten days. In addition to these medications, potassium permanganate soaks, gentian violet, 2 per cent thymol in olive oil and sulfanilimide dusting powder all failed to induce healing of the superficial lesions. In this case the diagnosis had been established by biopsy and successful cultural studies of material removed from the lip and the perianal region. At autopsy, lesions comparable to those of histoplasmosis were found in many organs and the adrenals were the site of caseation necrosis. The tissues were carefully examined by Dr. A. L. Amolsch, who is thoroughly familiar with histoplasmosis. He could not find organisms in the tissues after death, although he did find small clear areas of the size and shape of the capsule of Histoplasma capsulatum. It is possible that the infection had been cured by neostam or sulfathiazole and that the patient died of adrenal insufficiency.

27. Neostam (stibamine glucoside) was obtained from Burroughs-Wellcome & Co., Inc., New York city.

28. Mantel, cited by Meleney.[19a] Tompkins, R. D.: Personal communication to the authors.

29. Meleney, H. E.: Personal communication to the authors.

29a. Stilbamidine (4, 4-diamidinostilbene) was obtained from Merck & Co., Inc., Rahway, N. J.

30. Neostibosan (Bayer) is a pentavalent antimony compound, diethylamine paraaminophenylstibinate.

Among other substances that have been used in treatment are blood transfusions, potassium arsenite, neoarsphenamine, sulfarsphenamine, acetarsone, sulfanilimide, sulfadiazine, sodium thiosulfate, iodides, ionized metals, thymol, bone marrow, pentnucleotide, autogenous vaccines, ammonium and potassium tartrate, stibophen, quinine, and quinacrine hydrochloride. In general, their use has not altered the course of the disease. However, it should be emphasized that in many instances only small amounts of the substances were administered and these late in the course of the disease. Ultraviolet irradiation has been used unsuccessfuly on the superficial lesions.

Roentgen rays and radium have been used with results that seem equivocal. After a diagnosis of carcinoma of the tongue by biopsy in case 17, treatment with radium resulted in healing. The ulcer of the tongue recurred one year later and was treated with "superficial x-rays." Biopsy of this recurrent lesion showed Histoplasma capsulatum in the tissues. The ulcer healed, and the patient has shown no evidence of histoplasmosis for the past five years. In case 47, roentgen irradiation was used in the treatment of enlarged lymph nodes that were thought to be the site of lymphosarcoma. The nodes were much reduced in size. A later course of irradiation, also based on a supposition of lymphosarcoma, was given. As stated in the case report, lymphosarcoma was not found at autopsy, and since widely disseminated lesions of histoplasmosis were found, it can be said that we were treating histoplasmosis. It is our opinion that the second course of roentgen irradiation was deleterious. In case 71, roentgen therapy in fractionated doses was applied to large, exquisitely tender ulcers of the lip and tongue as well as over the region of ulcerated lesions in the pharynx. Nine hundred roentgens was given at each of several ports. During and following this treatment, tenderness of the ulcers of the tongue and lip disappeared and the lesions showed some reduction in size. Healing never occurred. The pharyngeal and laryngeal lesions showed no evidence of improvement following the treatment. Roentgen therapy has been used in several other cases without success.

Amputation was performed in a case of histoplasmosis of the knee (case 58), but the patient died nine days after the operation; so appraisal of this form of treatment is not possible.

OBSERVATIONS AT AUTOPSY

Autopsies were performed in 56 of the cases collected in this review. Since in several we had only fragmentary knowledge of the observations made, all of the figures given here are undoubtedly

low. They will be cited, nonetheless, since they indicate the relative liability of the various organs to involvement. In the table we have identified as instances of generalized histoplasmosis those cases in which the author stated that the involvement of the organs was generalized, and also those cases in which both the liver and the spleen as well as some other organ were involved. When the description of the case has stated that certain specific organs were involved, we have included the more important of these in the table.

It can be noted that 40 of the cases are listed as instances of generalized involvement. Specific mention of involvement of lymph nodes was found in 37 instances, while the lungs showed the lesions of histoplasmosis in at least 34. Of the remaining organs the adrenals were most frequently involved, lesions in them being mentioned 18 times. Caseation necrosis, which closely resembles that seen in tuberculosis, occurred in 11 cases (cases 10, 24, 28, 40, 43, 50, 52, 53, 60, 69 and 70). Lesions of the gastrointestinal tract occurred with moderate frequency and were found in all of the subdivisions of the tract. Such lesions were mentioned in 15 cases in this series, the lesions being found in the ileum or the colon most frequently. In many instances they took the form of large craterous ulcers, as in cases 2, 8, 43, 44 and 53. At other times, occasional foci of parasitized cells were found in the mucosa of the stomach and appendix, as in case 47. Lesions of the bone marrow were found in 16 instances. The kidneys were frequently involved, foci of infection being mentioned in 11 cases. In some cases small granulomatous areas were found in the interstitial tissue, while in others reticuloendothelial cells in the glomerular tufts were parasitized. Various lesions of the skin were described in 10 cases, but in several of these the direct connection between the infection with Histoplasma capsulatum and the lesions was not made clear.

As indicated previously, ulcerative lesions of the oral cavity are common. Lesions in the mouth were noted in 9 autopsies, and diagnosis of such lesions in 6 additional cases by biopsy has been made. The oral lesions in case 37 undoubtedly belong in this class, but they were not examined by biopsy. Lesions in the nose have been identified by biopsy or at autopsy in 6 cases. Histoplasmosis of the larynx has occurred at least 8 times. In 2 of these cases (cases 57 and 71) the initial lesion of the disease was on the tongue. Lesions have been found in the pancreas 6 times and in the thymus 4 times.

A vegetative endocarditis has been described in 3 cases. In case 63 the mitral and aortic valves were involved. The aortic valve was involved in case 21, while in case 71 the tricuspid valve was involved. In each of these cases Histoplasma capsulatum was found in the vegetations. A verrucous endocarditis of the tricuspid and aortic valves was found in case 4, but there is no statement as to its cause in the case report.

Lesions were found in the ear and brain in case 11, in the brain in case 21, in the parathyroids in case 53, in the prostate in case 23, in the trachea in cases 15 and 62 and in the knee joint and femur in case 58.

Miliary lesions resembling miliary tubercles have been found in at least 12 of the cases reviewed (cases 2, 22, 24, 34, 40, 47, 52, 53, 67, 69, 70 and 71). In cases 24, 34 and 70, active tuberculosis was also present, and it may have been the cause of the miliary lesions.

COMMENT

A review of the 56 cases of histoplasmosis which have been mentioned or described in the literature and of 15 cases which at the time of this review have not yet been published reveals a disease of worldwide distribution. Cases of the disease have appeared in 20 states and in the District of Columbia and in 10 countries outside the United States. The disease has been recognized in the United States at least 56 times, and 31, or more than half, of the cases have occurred in states lying along the Mississippi River and its main tributaries. Michigan is the only state in which a large number of cases of the disease have been recognized which does not fall into this group. If the cases observed there are added to the group, they bring to 41 the number of cases from the central area of the United States. We are unable to attribute definite significance to these facts or to the fact that no cases have been reported from the New England states.

Histoplasmosis has occurred in 51 white persons, 7 Negroes and 2 mulattoes. The number of cases of its occurrence in Negroes appears to be high in proportion to its incidence in white persons. This may indicate greater susceptibility on the part of the Negro. However, a large proportion of the cases in the United States has come from states having a relatively high Negro population. This and the occupations of the Negro are factors which must be considered carefully in this connection before a judgment is made.

A study of the sex incidence of histoplasmosis yields interesting results. We find that males and females are affected alike before the tenth year of life. In persons over 10 years, the disease

has occurred 7 times in males for every time it has been recognized in a female. A type of occupation involving exposure to the fungus in nature may be the determining factor. The effect of the gonads on susceptibility may be important, and it is interesting to note that of the 6 female patients older than 10 years of age, only 2 were less than 50. In other fungous diseases, such as actinomycosis, coccidiosis and sporotrichosis, infection of males is also more frequent.[31]

Histoplasmosis has occurred during the first year of life in 11 cases as frequently as it has occurred during any later decade. After the end of the first year the number of cases per decade is very low but shows gradual and progressive increases to reach a plateau in the fifth, sixth and seventh decades. In case 66, the fact that buccal ulcerations developed at the time that the child was weaned suggests that infection with the fungus was coincident with the start of bottle feeding. In 3 cases the disease manifested itself during the second month of life. This indicates that the fungus is most probably harbored by some member of the family or is closely associated with the environment in which the child lives. Up to the present, congenital infection with Histoplasma capsulatum, such as occurs with toxoplasma infection,[32] has not been evident in any case. In the future the use of the intradermal test [22] on the members of the family might help in studying the epidemiology of the disease. DeMonbreun,[25] Thuringer,[33a] Callahan,[33b] and Parsons and Everett [33c] found dogs naturally infected with Histoplasma capsulatum.

The occupations of 30 patients over 12 years of age were stated in the data available for the table. Ten of these were farmers, 4 were laborers, 2 were bartenders and 2 were waiters. The occupations of the remainder do not appear to be related, and it is felt that no definite conclusions can be drawn from these figures. It must be remembered that up to the present time the fungus has not been found in its vegetative form in nature.

The signs and symptoms of histoplasmosis show wide variation. They occurred (considering only the cases in which each sign or symptom was mentioned) as follows: Irregular, low or moderate fever was present in 47 of 49 cases; moderate to severe anemia of the hypochromic type, in 44 of 46 cases; palpable liver, in 39 of 51 cases; palpable spleen, in 37 of 51 cases; enlarged lymph nodes, in 29 of the 42 cases in which they were mentioned; leukopenia, in 28 of 48 cases; albuminuria, in 24 of 37 cases. Lesions of the lungs have been noted in 34 of the 61 cases analyzed; symptoms referable to the gastrointestinal tract, in 28 of the 61. Twenty-six of the 61 patients have shown loss of weight, and in 19 of these emaciation was described. Ulcerative lesions of the oropharynx were present in 21 of the 61; ulcerations of the skin, in 9; papular lesions, in 4, and lesions of the larynx, in 10. In case 32, external examination of the fundus of the eye showed lesions which were thought to be caused by Histoplasma capsulatum. In each of the 7 cases in which the values for blood proteins have been recorded they have been abnormal: low total protein in 3 cases and reversal of the albumin-globulin ration in 4.

Histoplasmosis may be a disease of long or of short duration. In more than four fifths of the cases the duration of symptoms averaged five months. In 3 cases, in all of which chronic ulcerative lesions of the skin were present, the infection appeared to have lasted for eight, ten and sixteen years before ending fatally. The patients of cases 17, 26, 57 and 59 are still living after intervals of two to six years. In 3 of these (cases 17, 57 and 59) ulceration of the tongue was the only demonstrable site of infection.

In attempting differential diagnosis one should remember that histoplasmosis mimics many more common diseases. It produces miliary lesions, ulcerations of the intestinal tract and caseation necrosis which resemble closely the same lesions produced by tuberculosis. It causes enlargement of the spleen, liver and lymph nodes such as one sees in leukemia and in Hodgkin's disease. In case 49 histoplasmosis and Hodgkin's disease occurred together. It has been confused with Banti's disease and atrophic cirrhosis. It produces ulcerative lesions of the oropharynx and larynx, and in several instances (cases 17, 53, 56 and 59) the clinical diagnosis before biopsy was carcinoma. In 3 cases Histoplasma capsulatum has been the cause of a vegetative endocarditis. The leukopenia and anemia must be differentiated as to causation from aleukemic leukemia and other blood dyscrasias. In cases of extreme hypotension, histoplasmosis must be thought of as a possible cause of adrenal insufficiency. Some

31. Jacobson, H. P.: Fungous Diseases: A Clinico-Mycological Text, Springfield, Ill., Charles C Thomas, Publisher, 1932.

32. Sabin, A. B.: Toxoplasma Neutralizing Antibody in Human Beings and Morbid Conditions Associated with It, Proc. Soc. Exper. Biol. & Med. **51**:6 (Oct.) 1942.

33. (*a*) Thuringer, J. M.: Histoplasmosis: Report of Its Occurrence in a Dog, Arch. Path. **37**:140 (Feb.) 1944. (*b*) Callahan, W. P., Jr.: Spontaneous Histoplasmosis Occurring in a Dog, Am. J. Trop. Med. **24**: 363 (Nov.) 1944. (*c*) Parsons, R. J., and Everett, M.: Histoplasmosis in a Dog: Report of a Case, to be published.

features of histoplasmosis very closely resemble the leishmanian infections, kala azar, cutaneous leishmaniasis and espundia. Smears, biopsies and cultures, done by persons acquainted with both infections, will be required for differentiation.

In the present series of cases, biopsy has been the most successful method of diagnosis during life. Biopsy with culture of the organism has been successful in many instances. Examination of the sternal bone marrow has shown the organisms in 5 cases and failed to show them in 4. Since the organisms have been found in blood smears in only 4 cases, this type of examination cannot be relied on for diagnosis. Invasion of the blood cells by sufficient numbers of organisms to be found readily in blood smears appears to occur late in the disease. Culture of the blood has yielded positive results in 9 instances. Examination by smear and by culture of the buffy coat of centrifuged blood might increase the ability to establish the diagnosis during life. Meleney [19a] has suggested that monocytes which are heavily parasitized might be heavier than the other cells and therefore might accumulate at the bottom of the centrifuge tube. Smear and culture of the sediment might prove diagnostic. In case 39 Histoplasma capsulatum was cultured from the sputum of a patient supposed to have tuberculosis. Cultural studies of the stools have been suggested by Crumrine and Kessel [11a] and by Henderson, Pinkerton and Moore,[34] in the belief that with extensive intestinal ulcerations Histoplasma capsulatum is probably present in the feces.

Histoplasmosis is a unique fungous disease. The yeastlike form of the fungus characteristically attacks or is attacked by the cells of the large macrophage, or reticuloendothelial, system. Since cells of this group are normally present in every tissue of the body (with the exception of cartilage and the cortex of bone), it is not surprising to find that parasitized macrophages may be found in any tissue. In the liver, the Kupffer cells are most frequently parasitized, and they undergo hypertrophy and hyperplasia. In some cases, e. g. case 53, a granulomatous process developed in the portal areas. In most of the other organs single macrophages may be found parasitized, or large numbers of them may be found forming one of the components of a granulomatous lesion. When the fungus induces a lesion on a surface, an ulcer with a granulomatous base is produced. When the lesion is within a tissue or organ, granulomas occur, which in some cases resemble miliary tubercles. The centers of the granulomatous lesions may undergo caseation necrosis. In the adrenals this process has been so advanced in several cases that death appears to have resulted from adrenal insufficiency.

34. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: Histoplasma Capsulatum as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. **118**:885 (March 14) 1942.

SUMMARY

A review of 71 cases of histoplasmosis reveals a fungous disease which is being found with increased frequency, particularly in the United States of America. Up to the present time, the disease has proved fatal in most instances.

The most common signs and symptoms, in the order of their decreasing frequency are: fever, hypochromic anemia, hepatomegaly, splenomegaly and lymphadenopathy. Anorexia and loss of weight are common. Ulceration of the oral mucosa (particularly the tongue), various types of cutaneous lesions and ulceration of the pharynx and larynx occur frequently. Other manifestations occur occasionally.

The yeastlike, or parasitic, form of the fungus characteristically is found in cells of the large macrophage, or reticuloendothelial, system. At autopsy, the organs are found to be involved in the following order in respect to frequency: spleen, liver, visceral lymph nodes, lungs, bone marrow, oral mucosa, adrenals, gastrointestinal tract, peripheral lymph nodes, kidneys and larynx. Vegetative endocarditis has occurred 3 times. Any or all of the remaining organs may be involved.

The disease affects persons of all ages. However, it has occurred in as many cases during the first year of life as in any later decade. The first, fifth, sixth and seventh decades of life have shown the greatest incidence of the disease. The sexes are equally affected up to and including the tenth year of life. After the tenth year, 7 out of 8 patients have been male.

The portal of entry of the fungus is still not known. More and more the evidence accumulating indicates that the mouth is the most frequent site of entrance. The large number of patients who have ulcerated lesions of the mouth, pharynx and gastrointestinal tract points to this conclusion. The many cases in which lesions of the nose, pharynx, larynx and lungs are present may be assembled as evidence that the respiratory tract is also a portal of entry. Another, and smaller, group of cases suggests entrance through the skin. The fungus is unknown in its vegetative form in nature, but the parasitic form has been identified in the dog.[38] What appears to be

the same organism has also been found in mice,[35] rats [36] and ferrets.[37]

Treatment of histoplasmosis is still in an experimental state. Certain antimony preparations and a new diamidine preparation (see section on treatment) appear to hold promise for the future.

Diseases which must be differentiated most frequently from histoplasmosis are tuberculosis, Hodgkin's disease, aleukemic leukemia and malignant neoplasms.

Successful antemortem diagnosis has most frequently been provided by histologic examination of biopsy material. Blood cultures, cultures of biopsy material and smears or scrapings from superficial lesions have been successful in several instances. Least successful of the laboratory methods used, although with a few outstanding exceptions, have been the examination of blood smears and that of sternal marrow. This statement should not cause the abandonment of these two methods, as they are simple and when successful are of great value.

NOTE.—Several papers [38] have come to our attention since this review was submitted for publication. Each contains the description of a case of histoplasmosis which has not been included in the present review.

35. Shortt, H. E.: The Pathogenicity of Insect Flagellates to Vertebrates, with Special Reference to Herpetomonas Ctenocephali, Fantham, Indian J. M. Research **10**:908 (April) 1923.

36. Sangiorgi, G.: Blastomicosi spontanea nei Muridi, Pathologica **14**:493 (Aug.) 1922.

37. Levine, N. D.; Dunlap, G. L., and Graham, R.: An Intracellular Parasite Encountered in Ferret, Cornell Vet. **28**:249 (July) 1938.

38. Boltjes, B.: Histoplasmosis: Report of a Case with Brief Review of the Literature, J. Kansas M. Soc. **44**:226 (July) 1943. Moore, M., and Jorstad, L. H.: Histoplasmosis and Its Importance to Otorhinolaryngologists: A Review with Report of a New Case, Ann. Otol., Rhin. & Laryng. **52**:779 (Dec.) 1943. Schlumberger, H. G., and Service, A. C.: A Case of Histoplasmosis in an Infant with Autopsy, Am. J. M. Sc. **207**:230 (Feb.) 1944.

RESPIRATION AND CIRCULATION IN PATIENTS WITH OBSTRUCTION OF THE SUPERIOR VENA CAVA

CEREBRAL FACTORS IN DYSPNEA AND ORTHOPNEA

M. D. ALTSCHULE, M.D.
BOSTON
A. IGLAUER, M.D.
CINCINNATI
AND
N. ZAMCHECK, M.D.
BOSTON

The signs of obstruction of the superior vena cava have aroused clinical interest since Stokes [1] described the syndrome over a century ago. The recent reviews of Ehrlich and others,[2] Ochsner and Dixon [3] and Hinshaw and Rutledge [4] discussed in detail the anatomic and clinical manifestations of this disorder. A number of authors [5] have described the findings on angiocardiography. The abnormal physical findings consist of striking venous engorgement, cyanosis and often edema, which are limited to the head, neck, arms and chest. Common complaints are headache, dizziness, fulness in the head, mental clouding and respiratory manifestations such as dyspnea, orthopnea and periodic breathing; in addition, paroxysmal dyspnea has been described by several authors,[6] and Ferris [7] reported "brief but severe attacks of hyperpnea" in 1 patient. The occurrence of respiratory symptoms in patients with stasis and with high venous pressure limited to the superior vena cava and its tributaries and with no congestion of the lungs affords an opportunity for study of factors important in the genesis of dyspnea and of orthopnea.

MATERIALS AND METHODS

Five male patients for whom a diagnosis of obstruction of the superior vena cava was made and who showed dyspnea, orthopnea or periodic breathing were studied; the periodic breathing was only moderately severe, no periods of apnea occurring. The patients ranged in age from 20 to 64 years. The diagnoses were as follows: mediastinal lymphoma (patients 1 and 3), mediastinal Hodgkin's disease (patient 2), metastatic carcinoma (patient 4) and syphilitic aneurysm of the aorta (patient 5). Additional studies were made of 3 of these patients after improvement occurred; 2 (patients 1 and 2) were studied when all manifestations of obstruction of the superior vena cava had disappeared after roentgen irradiation of the chest and the third (patient 3) after the symptoms had regressed spontaneously, only slight changes in the abnormal physical signs having taken place.

Studies of the respiratory dynamics were made with a Tissot spirometer or with a Benedict-Roth apparatus, with the patient sitting in bed. Venous pressure was measured by the method of Moritz and von Tabora,[8] the arm to

From the Medical Service and the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. Stokes, W.: A Treatise on the Diagnosis and Treatment of Diseases of the Chest: I. Diseases of the Lung and Windpipe, Dublin, Hodges and Smith, 1837, p. 231.

2. Ehrlich, W.; Ballon, H. C., and Graham, E. A.: Superior Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression, J. Thoracic Surg. **3**:352, 1934.

3. Ochsner, A., and Dixon, J. L.: Superior Vena Caval Obstruction: Review of the Literature and Report of Cases of Traumatic and Infectious Origin, J. Thoracic Surg. **5**:641, 1936.

4. Hinshaw, H. C., and Rutledge, D. I.: Lesions in the Superior Mediastinum Which Interfere with Venous Circulation, J. Lab. & Clin. Med. **27**:908, 1942.

5. (*a*) Taylor, H. K., and McGovern, T.: Evaluation of Angiocardiography, J. A. M. A. **121**:1270 (April 17) 1943. (*b*) Steinberg, I., and Robb, G. P.: Mediastinal and Hilar Angiography in Pulmonary Disease: A Preliminary Report, Am. Rev. Tuberc. **38**:557, 1938.

6. (*a*) Arrillaga, F. C., and Taquini, A. C.: Fisiopatogenia de la cianosis en los tumores del mediastino, Arch. urug. de med., cir. y especialid. **5**:305, 1934. (*b*) Lian, C., and Abaza, A.: La dissociation de la pression veineuse et de la vitesse circulatoire, signe caractéristique de l'obstruction de la veine cave supérieure, Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 730, 1935. (*c*) Erganian, J., and Wade, L. J.: Chronic Fibrous Mediastinitis with Obstruction of the Superior Vena Cava, J. Thoracic Surg. **12**:275, 1943.

7. Ferris, E. B., Jr.: The Effect of High Intracranial Venous Pressure upon the Cerebral Circulation and Its Relation to Cerebral Symptoms, J. Clin. Investigation **18**:19, 1939.

8. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

tongue time with sodium dehydrocholate,[9] the arm to lung time with ether [10] and the lung to brain time with carbon dioxide [11]; all of these studies were done with the patient recumbent. Measurements of cardiac output were made by the method of Starr and Gamble [12] with the patient sitting in bed. Studies of the blood gases were made by the method of Van Slyke and Neill.[13]

OBSERVATIONS

The respiratory dynamics were studied in 4 patients. When respiratory manifestations were present, the average respiratory rate ranged between 19 and 35, with an average for all of 24 per minute (table 1). After the disappearance of respiratory symptoms in 3 patients the rate was 14 to 16 per minute. The respiratory volume per minute when first studied ranged between 7.72 and 13.3 liters, with an average of 9.99 liters. After improvement had occurred in 3 patients the values were 5.86 to 7.2 liters per minute. The volume of tidal air was within the normal range, measuring 380 to 450 cc. when respiratory symptoms were present and 420 to 480 cc. after improvement had occurred.

The amount of carbon dioxide in the alveolar air ranged between 4.01 and 5.1 per cent, with an average of 4.58 per cent when first studied, and rose to 5.18 to 5.55 per cent after the disappearance of respiratory symptoms (table 1).

The oxygen saturation of the arterial blood was 92 to 94 per cent, irrespective of the presence or absence of respiratory symptoms (table 1).

The vital capacity was low in all 4 patients ranging between 900 and 2,500 cc. when first studied (table 1). After the disappearance of respiratory symptoms the vital capacity was unchanged in the 1 patient (no. 3) in whom improvement was spontaneous and increased slightly in the 2 (nos. 1 and 2) in whom improvement followed roentgen irradiation.

TABLE 1.—*Studies of Respiratory Dynamics*

Patient	Respirations per Min.	Tidal Air, Cc.	Respiratory Volume, L/min.	Alveolar Air Carbon Dioxide, per Cent	Arterial Blood Oxygen Saturation, per Cent	Vital Capacity, Cc.	Comments
1	19	405	7.72	5.10	93	2,500	Orthopnea
	14	420	5.86	5.55	92	2,800	No orthopnea
2	19	440	8.36	4.83	93	1,210	? orthopnea; periodic breathing
	14	480	6.32	5.21	94	1,650	No periodic breathing or orthopnea
3	23	450	10.36	4.36	94	1,700	Periodic breathing
	16	450	7.20	5.18	..	1,700	No periodic breathing
4	35	380	13.30	4.01	..	900	Dyspnea at rest; orthopnea

TABLE 2.—*Studies of Venous Pressure and Circulation Time*

Patient	Venous Pressure, Cc.		Circulation Time, Seconds			Comments
	Antecubital	Femoral	Arm to Tongue (Sodium Dehydrocholate)	Arm to Lung (Ether)	Lung to Brain (Carbon Dioxide)	
1	27	..	29	17	10	Orthopnea
	8	8	17	..	9	No orthopnea
2	37	..	25	..	..	Periodic breathing, ? orthopnea
	4	..	17	..	..	No periodic breathing or orthopnea
3	29	8	28	..	8	Periodic breathing
	22	..	26	..	..	No periodic breathing
4	32	4	*	..	..	Dyspnea at rest, orthopnea
5	23†	5	35‡	..	..	Dyspnea at rest, orthopnea

* No end point.
† Spinal fluid pressure was 337 mm.
‡ The femoral vein to tongue time was 17 seconds.

9. Winternitz, M.; Deutsch, J., and Brüll, Z.: Eine klinischbrauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, Med. Klin. **27**:986, 1931.

10. Hitzig, W. M.: Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, Proc. Soc. Exper. Biol. & Med. **31**:935, 1934.

11. Gubner, R.; Schnur, S., and Crawford, J. H.: The Use of CO_2 Inhalation as a Test of Circulation Time. J. Clin. Investigation **18**:395, 1939.

12. Starr, I., Jr., and Gamble, J. C.: An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, Am. J. Physiol. **87**: 450, 1928.

13. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

The pressure in the antecubital veins ranged from 23 to 27 cc. of water when the patients showed respiratory symptoms; at this time the pressure in the femoral vein was 4 to 8 cm. of water (table 2). When the respiratory symptoms of 2 patients (nos. 1 and 2) disappeared after roentgen radiation, the antecubital venous pressure fell to normal. The patient in whom spontaneous regression of hyperventilation and periodic breathing occurred showed a fall in antecubital venous pressure of only 7 to 22 cm. of water.

The circulation time between arm and tongue was prolonged, measuring twenty-five to thirty-five seconds when the patients had respiratory symptoms; the femoral to tongue time was normal (table 2). The arm to tongue time fell to the normal value of seventeen seconds in the 2 patients (nos. 1 and 2) who improved after roentgen irradiation and showed no significant

TABLE 3.—*Studies of Cardiac Output and Blood Gases*

	Cardiac Output		Arteriovenous Oxygen Difference, Vol. per Cent		
		L/100 Cc.			
Patient	L/Min.	O_2	Arm	Leg	Comments
1	3.84	1.75	9.8	5.6	Orthopnea
	3.91	1.72	4.6	...	No orthopnea
2	....	....	8.5	...	* Periodic breathing; † orthopnea
	....	....	5.6	...	No periodic breathing or orthopnea
3	4.70	1.57	10.4	8.5	Periodic breathing
	....	....	6.9	...	No periodic breathing

change in the patient (no. 3) who improved spontaneously. A single measurement of arm to lung time was abnormally prolonged when the arm to tongue time was slowed. The lung to brain time was not abnormal at any time.

The cardiac output of 2 patients (nos. 1 and 3) was normal when respiratory symptoms were present, and that of 1 of them was normal after these symptoms had disappeared (table 3).

The local arteriovenous oxygen differences were calculated from measurements made on blood taken from the femoral artery and from the femoral and antecubital veins (table 3). When respiratory symptoms were present, the arteriovenous difference was increased in the upper extremities and was normal in the lower. There was a decrease in arteriovenous oxygen difference in the arms of all 3 patients studied after regression of respiratory symptoms.

COMMENT

A number of authors have studied venous pressure in patients with obstruction of the superior vena cava, and all are agreed that the pressure in the tributaries of the superior cava is elevated,[14] while that in the veins draining into the inferior cava is normal.[15] The results of the present study corroborate these earlier observations. Burwell [14m] found, in addition, that the pressure in the collateral veins over the chest is intermediate between that in the upper and that in the lower extremities. Only a few reports on the circulation time in this syndrome are available. In most of the cases studied slowing of the arm to tongue time was noted,[16] although Hitzig [14k] found it normal or only slightly slowed. The contention of Lian and Abaza [6b] that the arm to tongue circulation time is always normal and that this "dissociation" between a high venous pressure and a normal circulation time is diagnostic of obstruction of the superior vena

14. (*a*) Ehrlich, Ballon, and Graham.[2] (*b*) Ochsner and Dixon.[3] (*c*) Hinshaw and Rutledge.[4] (*d*) Lian and Abaza.[6b] (*e*) Erganian and Wade.[6c] (*f*) Ferris.[7] (*g*) Bürger: Ueber die klinische Bedeutung des Valsalvaschen Versuches, München. med. Wchnschr. **68**:1066, 1921. (*h*) Kroetz, C.: Die Koeffizienten des klinisch messbaren Venendruckes, Deutsches Arch. f. klin. Med. **139**:325, 1922. (*i*) Villaret, M., and Martiny, M.: Étude de la pression veineuse périphérique dans les syndromes médiastinaux: Son intérêt de controle pour le diagnostic et le prognostic, Presse méd. **37**:249, 1929. (*j*) Villaret, M., and Desoille, H.: Exemples cliniques montrant l'intérêt général de la phlébopiézométrie au point de vue du diagnostic, du prognostic et de la thérapeutique, ibid. **40**:1477, 1932. (*k*) Hitzig, W. H.: The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, Am. Heart J. **10**:1080, 1935. (*l*) Ferris, E. B., Jr., and Wilkins, R. W.: The Clinical Value of Comparative Measurements of the Pressure in the Femoral and Cubital Veins, ibid. **13**:431, 1937. (*m*) Burwell, C. S.: A Comparison of the Pressures in Arm Veins and Femoral Veins with Special Reference to Changes During Pregnancy, Ann. Int. Med. **11**:1305, 1938. (*n*) Hussey, H. H.: The Effect of Mediastinal Lesions on Pressures in the Antecubital and Femoral Veins, Am. Heart J. **17**:57, 1939. (*o*) Rutledge, D. I., and Gray, H. K.: Indeterminate Type of Obstruction of the Superior Vena Cava, Proc. Staff Meet., Mayo Clin. **14**:337, 1939. (*p*) Veal, J. R., and Hussey, H. H.: The Use of Exercise Tests in Connection with Venous Pressure Measurements for the Detection of Venous Obstruction in the Upper and Lower Extremities, Am. Heart J. **20**:308, 1940. (*q*) Gray, H. K., and Skinner, I. C.: Constrictive Occlusion of the Superior Vena Cava, Surg., Gynec. & Obst. **72**:923, 1941. (*r*) Eyster, J. A. E., and Middleton, W. S.: Clinical Studies on Venous Pressure, Arch. Int. Med. **34**:228 (Aug.) 1924. (*s*) Porot, M. A.: Les fortes hypertensions céphalorachidiennes d'origine veineuse, Rev. neurol. **1**:1173, 1930. (*t*) Smirk, F. H.: Observations on the Causes of Oedema in Congestive Heart Failure, Clin. Sc. **2**:317, 1936. (*u*) Wartman, W. B.: A Study of the Venous Pressure in Some Common Diseases, Am. J. M. Sc. **190**:464, 1935.

15. Ochsner and Dixon.[3] Hinshaw and Rutledge.[4] Erganian and Wade.[6c] Ferris.[7] Villaret and Martiny.[14i] Ferris and Wilkins.[14l] Burwell.[14m] Hussey.[14n] Rutledge and Gray.[14o] Veal and Hussey.[14p] Gray and Skinner.[14q] Eyster and Middleton.[14r]

16. Ehrlich, Ballon, and Graham.[2] Rutledge and Gray.[14o] Gray and Skinner.[14q]

cava is not supported by the findings of the aforementioned authors or by those of the present study. The additional studies made here of arm to lung, femoral vein to lung and lung to brain times show that the slowing is on the venous side of the circulation in the upper part of the body; Hitzig [14k] also found some slowing on the venous side in his patients.

The significance of the slowed venous circulation time may be different under various circumstances. Since the arm to tongue and arm to lung time represent time elapsed during the passage of blood from a vein to the end organ, it cannot be determined from this measurement whether the blood is flowing slowly or is taking a long and circuitous path through the inferior cava or both. In this connection it is of interest that patient 3 of the present study showed a slight fall in venous pressure and a return of the arteriovenous oxygen difference to normal, with no change in circulation time. It is considered, therefore, that the first measurements made on this patient are a reflection of stasis, while the results of the later studies suggest that enough collateral circulation developed to overcome the stasis, the prolonged circulation time on this occasion being an indication of the length of the pathway back to the heart. It should be borne in mind also that elevation of the venous pressure consequent to obstruction does not necessarily indicate slowing of flow in the obstructed vein or in the capillaries draining into it. Stewart [17] has shown that such obstruction may cause the flow of blood to decrease initially, with a return to normal when enough pressure has been built up in the veins.

In all 3 of the patients described by Arrillaga and Taquini,[6a] in 1 (no. 1) of the 5 described by Ferris [7] and in all 3 studied here while manifesting respiratory symptoms, studies of the arteriovenous oxygen difference indicate stasis in the tissues drained by the superior cava. On the other hand, in 4 (nos. 2, 3, 4 and 5) of Ferris' patients [7] with no respiratory symptoms and in 1 (patient 3) studied here after spontaneous improvement of symptoms, the observations show that no stasis in the tissues existed, apparently because an adequate venous collateral circulation had developed. The development of this collateral circulation, with a resultant late fall in venous pressure toward normal some time after ligation of the superior vena cava, has been studied in the dog by Carlson.[18]

17. Stewart, G. N.: Studies on the Circulation in Man: I. Measurement of the Bloodflow in the Hands, Heart **3**:33, 1911; The Effect of Bandaging of the Legs on the Rate of Blood Flow in the Feet, Arch. Int. Med. **19**:335 (March) 1917.

18. Carlson, H. A.: Obstruction of the Superior Vena Cava, Arch. Surg. **29**:669 (Oct.) 1934.

The data of the present study and of the earlier work reviewed provide the basis for an understanding of the mechanism of the signs and symptoms occurring in patients with obstruction of the superior vena cava. The cyanosis in all patients with the syndrome is consequent to increased prominence of the cutaneous veins [19] and in many is accentuated by abnormally great deoxygenation of capillary blood due to stasis; arterial unsaturation caused by obstruction to breathing is not a factor in the uncomplicated case, as was pointed out by Arrillaga and Taquini.[6a] The edema of the upper part of the body is at least in part the result of high venous pressures. The role of high filtration pressures in the genesis of edema has been studied by Landis [20] and others.[21] Nevertheless the fact that in spite of high venous pressures the edema may be intermittent [14q] or completely absent [21a] suggests that anoxia due to stasis may also be a factor.

The respiratory manifestations of obstruction of the superior cava seen in the patients studied here consisted of periodic breathing, constant hyperventilation, dyspnea at rest and on exertion and orthopnea. The observation of periodic breathing is not surprising: Its occurrence in patients with increased spinal fluid pressure is well known, and it has been produced in animals by raising the intracranial pressure.[22] Increases in the latter always result when the venous pressure in the head is high. Bürger [14g] and Porot [14s] found the spinal fluid pressure increased in a patient with obstruction of the superior vena cava, and Ferris [7] later made the same observation in his 5 patients; these earlier findings are corroborated in the present study (table 2). However, only 1 of Ferris' [7] patients had "periods of

19. Goldschmidt, S., and Light, A. B.: Cyanosis, Unrelated to Oxygen Unsaturation, Produced by Increased Peripheral Venous Pressure, Am. J. Physiol. **73**:173, 1925.

20. Krogh, A.; Landis, E. M., and Turner, A. H.: The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood, J. Clin. Investigation **11**:63, 1932. Landis, E. M.; Jonas, L.; Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, ibid. **11**:717, 1932. Landis, E. M., and Gibbon, J. H.: The Effects of Temperature and of Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, ibid. **12**:105, 1933.

21. Mende: Ueber Hyperämie und Oedem bei der Hemmung des Rückflusses des venösen Blutes durch die Staubinde, Deutsche Ztschr. f. Chir. **150**:379, 1919. Drury, A. N., and Jones, N. W.: Observations upon the Rate at Which Oedema Forms When the Veins of the Human Limb Are Congested, Heart **14**:55, 1927.

21a. Hinshaw and Rutledge.[4] Smirk.[14t]

22. Greeley, C. E., and Greeley, P. O.: Circulatory Changes During Periodic Ventilation with Apnea Produced by Marked Curtailment of Blood Flow to the Brain, Am. J. Physiol. **95**:263, 1930.

hyperpnea." As was pointed out by Arrillaga and Taquini,[6a] patients with obstruction of the superior vena cava show lowering of the level of carbon dioxide in the arterial blood; the observations made here on the amount of carbon dioxide in the alveolar air are in accord with their findings. The importance of lowered levels of carbon dioxide in the arterial blood in the genesis of periodic breathing is generally accepted.[23] Anoxia of the respiratory center must exist in many patients with obstruction of the superior vena cava, but the role of such anoxia in the causation of periodic breathing is not established.[23c] No attempt will be made to explain the occurrence of paroxysmal dyspnea in this syndrome, since it is not clear from the published reports [24] whether the phenomena observed were true paroxysmal dyspnea or merely a manifestation of periodic breathing.

The possible relation of impaired flow through the respiratory center to hyperventilation, dyspnea and orthopnea in cardiac decompensation has been the subject of much controversy, in spite of the demonstration that in animals slow flow through the brain causes hyperventilation [25a]; in addition Calhoun and others [25b] observed increased respiratory activity after jugular obstruction in human beings. Accordingly, the occurrence of these symptoms in persons in whom there is stasis in the brain and not in the lungs is of great importance. In the work of Arrillaga and Taquini,[6a] as well as in the present study, there is a striking correlation between the occurrence of hyperventilation, dyspnea and orthopnea and changes in the gases of the blood which are indicative of stasis in the upper part of the body. This finding is in harmony with the data of Ferris,[7] who noted no such respiratory abnormalities and no evidence of cerebral stasis in most of his patients with obstruction of the superior vena cava. The relationship between stasis in the tissues and hyperventilation is especially well illustrated by patient 3 of the present study: The disappearance of symptoms in this patient was paralleled by the disappearance of evidences of tissue stasis apparently as a consequence of the development of collateral circulation, while the venous pressure and the circulation time showed no striking change. It might be objected that in the patients of the present series respiratory symptoms may have developed because of the presence of masses of appreciable size within the thorax, as evidenced by roentgenographic findings and by low vital capacities. However, the latter showed little or no change when hyperventilation disappeared. Moreover, in many of the reported cases with respiratory manifestations [26] the cause of the obstruction of the superior vena cava was either thrombosis or pressure by a mass far too small to interfere with pulmonary function.

Another possible objection to the acceptance of slow flow through the brain as a cause for the dyspnea and hyperventilation studied here may be found in the reports that distention of the great veins may cause reflex hyperventilation.[27] However, the work on which the latter conclusion is based is not entirely acceptable in that conclusive proof is lacking that slowing of flow through the brain did not occur in those experiments. Moreover, in some of the reported cases in which dyspnea and orthopnea occurred, for instance, case 1 of Ochsner and Dixon,[3] distention of the superior cava could not have occurred because the vein was thrombosed in its entire length. It is therefore concluded that the weight of evidence favors the opinion expressed by Arrillaga and Taquini [6a] that a cause of hyperventilation and dyspnea in the syndrome of obstruction of the superior vena cava is slowed flow leading to tissue stasis in the respiratory center. Since the stasis is aggravated by recumbency, orthopnea is readily understandable. In the case of those patients in whom dyspnea is present only on exertion, it is likely that the general rise in venous pressure accompanying exercise de-

23. (*a*) Pembrey, M. S., and Allen, R. W.: Observations upon Cheyne-Stokes Respiration, J. Physiol. **32**:xviii, 1905. (*b*) Douglas, C. G., and Haldane, J. S.: The Causes of Periodic or Cheyne-Stokes Breathing, ibid. **38**:401, 1909. (*c*) Anthony, A. J.; Cohn, A. E., and Steele, J. M.: Studies on Cheyne-Stokes Respiration, J. Clin. Investigation **11**:1321, 1932. (*d*) Harrison, T. R.; King, C. E.; Calhoun, J. A., and Harrison, W. G., Jr.: Congestive Heart Failure: XX. Cheyne-Stokes Respiration as the Cause of Paroxysmal Dyspnea at the Onset of Sleep, Arch. Int. Med. **53**:891 (June) 1934.

24. Arrillaga and Taquini.[6a] Lian and Abaza.[6b] Erganian and Wade.[6c] Ferris.[7]

25. (*a*) Greeley and Greeley.[22] Gesell, R.: The Chemical Regulation of Respiration, Physiol. Rev. **5**:551, 1925. Schmidt, C. F.: The Influence of Cerebral Blood-Flow on Respiration: I. The Respiratory Responses to Changes in Cerebral Blood-Flow, Am. J. Physiol. **84**: 202, 1928. (*b*) Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. L., and Tims, M. M.: Studies in Congestive Heart Failure: XIV. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, J. Clin. Investigation **10**:833, 1931.

26. Ehrlich, Ballon, and Graham.[2] Ochsner and Dixon.[3] Hinshaw and Rutledge.[4] Erganian and Wade.[6c] Rutledge and Gray.[14o] Gray and Skinner.[14q]

27. Harrison, T. R.; Harrison W. G., Jr.; Calhoun, J. A., and Marsh, J. P.: Congestive Heart Failure: XVII. The Mechanism of Dyspnea on Exertion, Arch. Int. Med. **50**:690 (Nov.) 1932. Harrison, T. R.; Harrison, W. G., Jr., and Marsh, J. P.: Reflex Stimulation of Respiration from Increase in Venous Pressure, Am. J. Physiol. **100**:417, 1932. Megibow, R. S.; Katz, L. N., and Feinstein, M.: Kinetics of Respiration in Experimental Pulmonary Embolism, Arch. Int. Med. **71**:536 (April) 1943.

creases the differential between the high pressure above the obstruction and the lower pressure below it necessary for the maintenance of flow through the collateral vessels, thereby aggravating the stasis in the brain. A corollary to the foregoing conclusion is that cerebral stasis is a cause of hyperventilation and dyspnea in cardiac decompensation; it is considered that the concept that increased venous pressure favors orthopnea [28] is supported by the results of the present study. It is not to be concluded, however, that congestion of the lungs may be minimized as a factor in the symptoms of cardiac decompensation; the role of the pulmonary changes in congestive failure in the causation of hyperventilation and dyspnea [29] and of orthopnea [30] has been discussed at length elsewhere.

It has been shown [31] that orthopnea in patients with cardiac disease is aggravated by a high spinal fluid pressure, and accordingly the question arises as to whether high intracranial pressure might not be the cause of the orthopnea occurring with obstruction of the superior vena cava. However, the aforementioned parallelism between the presence of orthopnea and the evidences of stasis and the lack of close correlation between the occurrence of that symptom and high spinal fluid pressures suggest that at most intracranial pressure exerts only a contributory influence. In addition, it has been shown [32] that elevation of the intracranial pressure may by itself slow the flow of blood through the brain.

28. Ernstene, A. C., and Blumgart, H. L.: Orthopnea: Its Relation to Increased Venous Pressure of Myocardial Failure, Arch. Int. Med. **45**:593 (April) 1930.

29. Altschule, M. D.: The Pathological Physiology of Chronic Cardiac Decompensation, Medicine **17**:75, 1938.

30. Altschule, M. D.; Zamcheck, N., and Iglauer, A.: The Lung Volume and Its Subdivisions in the Upright and Recumbent Positions in Patients with Congestive Failure: Pulmonary Factors in the Genesis of Orthopnea, J. Clin. Investigation **22**:805, 1943.

31. Harrison, W. G., Jr.: The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea, J. Clin. Investigation **12**:1075, 1933; Cerebrospinal Fluid Pressure and Venous Pressure in Cardiac Failure and the Effect of Spinal Drainage in the Treatment of Cardiac Decompensation, Arch. Int. Med. **53**:782 (May) 1934. Robertson, H. F., and Fetter, F.: The Effects of Venesection on Arterial, Spinal Fluid and Venous Pressures with Especial Reference to Failure of the Right and Left Heart, J. Clin. Investigation **14**:305, 1935.

SUMMARY AND CONCLUSIONS

A study of the respiratory and cardiovascular dynamics in 5 patients with obstruction of the superior vena cava revealed that hyperventilation, with a consequent fall in alveolar carbon dioxide, often occurs in this syndrome. Stasis may be present in the brain of a patient with obstruction of the superior vena cava. High venous pressure and slowed circulation time do not necessarily indicate the presence of stasis. Studies of the blood gases are more helpful in this regard.

It is concluded that the occurrence of hyperventilation, dyspnea, orthopnea or periodic breathing in a patient with obstruction of the superior vena cava is associated with tissue stasis in the brain.

330 Brookline Avenue.

32. Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN CAUSE, WITH UNUSUAL MANIFESTATIONS AND COMPLICATIONS

MAJOR ROBERT E. GLENDY, CAPTAIN SAMUEL B. BEASER
AND CAPTAIN WALTER D. HANKINS
MEDICAL CORPS, ARMY OF THE UNITED STATES

The growing volume of reports [1] concerning primary atypical pneumonia attests to the interest in this condition. It is not a contagious disease, but it does occur in epidemic form, which may account for the actual increase in the number of cases. Furthermore, the attention which has been focused on the disease has revealed cases that otherwise might have been overlooked. It is noteworthy that the 150 cases of pneumonia [2] which form the basis of this report were derived from a total of 180 cases of pneumonia of all types encountered at an army station hospital from Sept. 1, 1942 to June 1, 1943. In view of our clinical experience, five sixths seems to be a high proportion of unclassifiable pneumonia, which may in part be due to the younger age group of the patients.

Among these 150 cases certain unusual manifestations appeared, as follows: meningismus in 3 cases, pleural effusion in 4, marked leukopenia in 1, spontaneous pneumothorax and simulating tuberculosis in 1, pulmonary abscess in 4 and late secondary infection in 2.

CASES WITH MENINGITIS

CASE 1.—*History.*—A white man aged 24 was admitted to the hospital on Nov. 29, 1942 and discharged on Dec. 19. His past history was irrelevant. The present illness began three days before he entered the hospital, with abrupt onset of shaking chills, weakness, pains in the muscles of the legs, back and ankles and cough productive of green sputum. Severe pounding frontal headache began four hours before his admission and nausea the night before.

Physical Examination.—The patient was acutely ill, with his skin flushed and his lips cyanotic. He had no cutaneous lesions. There was moderate stiffness of the neck. He kept his eyes partly closed, although he said he did not suffer from photophobia. A slight nasal discharge and conjunctival injection were noted. The chest was clear. There was no cardiovascular disease. The Kernig sign was slightly positive.

Laboratory Examinations.—At a lumbar puncture made on November 29, the fluid flowed more freely than normally. It contained 1 lymphocyte per high power field; the globulin was not increased; the total protein content was 25.6 mg. per hundred cubic centimeters and the sugar content 80 mg.; the Wassermann reaction was negative and the colloidal gold curve 0000000000; culture gave negative results. On December 2 there were 6 lymphocytes per high power field; the globulin was not increased; the sugar content was 74 mg. per hundred cubic centimeters, and there was no growth on culture. On December 6 the fluid contained 3 lymphocytes per high power field; the sugar content was 70 mg. per hundred cubic centimeters; the globulin was not increased, and culture gave negative results. Blood counts were as follows: November 30, 85 per cent hemoglobin, 4,400,000 erythrocytes and 13,750 leukocytes, with 65 per cent polymorphonuclear cells, 30 per cent lymphocytes and 5 per cent eosinophils; December 2, 9,000 leukocytes, with 73 per cent polymorphonuclear cells, 26 per cent lymphocytes and 1 per cent eosinophils. On December 3 the sputum showed occasional pneumococci. Culture and the Kahn test of the blood gave negative results. Culture of material from the throat showed no meningococci.

Roentgenograms of Chest.—On November 29, a triangular area of infiltration was seen in the upper lobe of the left lung. Five days later this area was still present and in addition a small area was present in the upper lobe of the right lung. Twelve days after the second examination the chest was almost entirely clear.

Course.—The temperature on the patient's admission was 104 F.; it rose to 105 F. the same day and then came down, by lysis, to normal by the sixth day. There was a slight rise to 99.6 F. on the thirteenth, fourteenth and fifteenth days of the illness, coinciding with sore throat. Culture of material from the throat at that time showed hemolytic streptococci, and the white blood cell count was 12,000. The pulse rate was 100 to 110 and then dropped to normal with the temperature. The respiratory rate was 25 to 30 for three days and then became normal. The patient was lethargic on admission and hazy mentally. This condition, together with the headache, completely disappeared in about a week. His cough became much more productive, and rales devel-

1. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonia with a Brief Résumé of Recent Discoveries, Arch. Int. Med. **70**:513 (Oct.) 1942. Dingle, J. H.; Abernethy, T. J.; Badger, G. F.; Buddingh, G. J.; Feller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, W. B., Jr.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223 (March) 1943. Campbell, T. A.; Strong, P. S.; Grier, G. S., III, and Lutz, R. J.: Primary Atypical Pneumonia: A Report of Two Hundred Cases at Fort Eustis, Virginia, J. A. M. A. **122**:723 (July 10) 1943.

2. The diagnosis of primary atypical pneumonia was applied in cases in which there was definite pulmonary involvement on roentgenography, frequently with severe headache and leukocytosis with a white cell count not exceeding 15,000, and in which pneumococcic and other types of pneumonia were excluded by laboratory data or the clinical course.

oped at the bases of both lungs and over the left upper quadrant of the chest. On the fourth day the chest was clear on physical examination. The stiffness of the neck was gone in a week. The patient's feeling of well-being returned, together with his appetite, on about the sixth day in the hospital, this improvement coinciding with a drop of temperature to normal. He received sulfadiazine, 7 Gm. the first day, 6 Gm. a day on the second, third, fourth, fifth and sixth days and 4 Gm. on the seventh, eighth and ninth days.

This case illustrates, additionally, the complete ineffectiveness of sulfadiazine therapy in primary atypical pneumonia and infection of the throat by secondary invaders late in the disease.

CASE 2.—A white man aged 26 was admitted to the hospital on Nov. 15, 1942 and discharged December 11.

History.—The past history was irrelevant. His present illness began two days before his admission, with sudden onset of severe postorbital pounding headache, cough, shaking chills and perspiration. His throat was slightly sore. He had anorexia, and his "stomach felt weak." There were cramps in the calves of the legs and once, on the day of the patient's admission, in the right thigh.

General Examination.—The patient was mentally confused, repeating words and phrases both of the questions and of his answers. He was slightly disoriented and complained of vertigo. There was no stiffness of the neck. Definite photophobia was noted, and the conjunctivas and scleras were injected. The blood pressure was 115 systolic and 80 diastolic. Both calves were tender, and the feet were held in the extended position and resisted flexion, which, however, could be accomplished with effort. The reflexes were hyperactive. The right knee jerk was greater than the left; the Oppenheim sign was present on the left side, and the Kernig sign was also elicited.

Laboratory Examination.—Lumbar puncture was done on November 16. The spinal fluid obtained contained 6 lymphocytes per high power field; the globulin was not increased; the total protein content was 42 mg. per hundred cubic centimeters; the colloidal gold curve was 1111100000; the Wassermann reaction was negative. On November 23 a second lumbar puncture was done. The fluid then contained 33 lymphocytes per high power field; the sugar content was 63 mg. per hundred cubic centimeters; the globulin was increased, and culture gave negative results. On November 16 the sputum was found to contain a few pneumococci, not typable. Blood counts were as follows: November 16, 12,000 leukocytes, with 72 per cent polymorphonuclear cells, 26 per cent lymphocytes and 2 per cent monocytes; November 23, 9,650 leukocytes, with 69 per cent polymorphonuclear cells, 23 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils; November 25, 85 per cent hemoglobin, 4,800,000 erythrocytes and 14,400 leukocytes, with 75 per cent polymorphonuclear cells, 24 per cent lymphocytes and 1 per cent eosinophils; November 30, 14,000 leukocytes; December 2, 8,800 leukocytes, with 72 per cent polymorphonuclear cells, 23 per cent lymphocytes, 1 per cent monocytes and 4 per cent eosinophils. The Kahn reaction of the blood was negative.

Roentgenograms of Chest.—On November 16 there was a triangular area of infiltration in the mesial portion of the base of the right lung. Eleven days later the infiltration was more extensive. It cleared in about ten more days.

Course.—The temperature on the patient's admission was 105 F.; it came down to normal in three days, then rose to 104 F. on the fifth day and followed a remittent course from normal up to 101 or 102 F. through the eleventh day. It became normal on the twelfth day. The pulse rate was 120 the first day and came down to normal along with the temperature. The respiratory rate was normal throughout.

On the third day, the patient had diminished breath sounds at the base of the right lung and was still confused mentally. During the night he had restless sleep with a short period of hallucinations. On the fifth day, with rise of temperature, mental confusion increased and there was slight stiffness of the neck, with headache, vertigo and photophobia persistent. On the eighth day, the neck was still slightly stiff; there were slight headache and a little drowsiness but no photophobia. On the ninth day, after a lumbar puncture the previous day, all symptoms improved. On the tenth day, the patient suffered from slight headache and vertigo only when sitting up; there was no photophobia. On the twelfth day—the cough had been increasing all week—vesicular breath sounds and rales were present at the base of the right lung. Since the ear drums were red, administration of sulfadiazine was started. On the seventeenth day, the patient's mental condition was rapidly improving, and his family said that he seemed completely normal mentally again.

This case is of particular interest because of the presence of leukocytes in the spinal fluid. Additionally, it illustrates secondary infection of the middle ear late in the disease.

THREE CASES WITH PLEURAL EFFUSION

These cases are of interest mainly from the roentgenologic point of view, but clinically it was noted that they were usually the cases of severe symptoms with a good deal of prostration, a high, remittent type of fever and a strong tendency to relapse, especially if the patient was allowed to get out of bed before the fluid had been completely resorbed.

CASE 3.—A white man aged 27 was admitted to the hospital on Dec. 4, 1942 and discharged on Feb. 9, 1943.

History.—The patient had had pneumonia four years previously, in the right lung. For one week the patient had had a "head cold," and for twenty-four hours before admission he had suffered from cough, severe headache and generalized malaise. Just prior to admission he had a shaking chill and sharp pain in the lower part of the chest on the right side.

Physical Examination.—The patient was prostrated. He had a nasal discharge and suppression of breath sounds at the base of the right lung.

Laboratory Examinations.—Culture of the sputum on December 5 revealed no pneumococci. On January 3 there was an abundant growth of hemolytic staphylococci; on January 18, of Staphylococcus aureus. Leukocyte counts were as follows: December 5, 8,500; December 12, 9,300; December 19, 15,500; December 26, 13,400, with 72 per cent polymorphonuclear cells; January 14, 16,050, with 81 per cent polymorphonuclear cells; January 22, 11,000; January 27, 8,550. The urine and the Kahn reaction of the blood were normal. An electrocardiogram made on December 29 showed sinus tachycardia.

Roentgenograms of the Chest.—On December 5 a hazy area at the base of the right lung was seen, which was consistent with atypical pneumonia; six days later the

infiltration was denser and more extensive; one month later (fig. 1) the infiltration was still present and there was a small amount of fluid. The chest finally became normal nine weeks from the onset.

Course.—The patient's temperature on admission was 100 F. It fluctuated between normal and 103 F. for the first fifteen days, stayed around 99 F. until the twenty-second day, again fluctuated up to 103 F. until the thirty-third day and then dropped to normal and remained so.

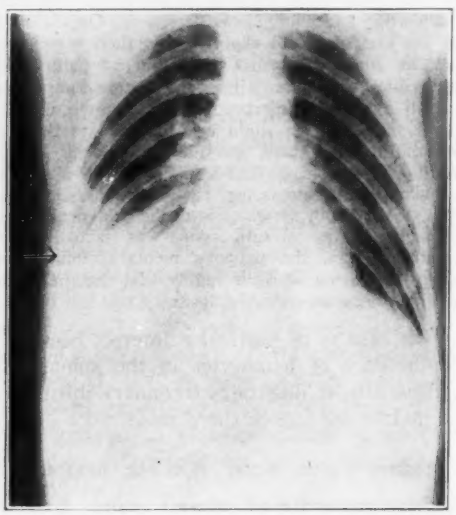

Fig. 1 (case 3).—Fluid at the base of the right lung still present one month after the onset of pneumonia.

CASE 4.—A white man aged 30 was admitted to the hospital on March 14, 1943 and discharged on April 3.

History.—The past history was irrelevant. He had had a dry cough for four days and for one day had suffered from acute malaise, a temperature of 104 F. and increased cough. He was given 5 Gm. of sulfathiazole the day before admission.

Physical Examination.—The right sclera was injected. The pharynx was red, and there was a slight nasal exudate. The lungs showed dulness, bronchial breath sounds and rare post-tussive rales at the base of the left lung.

Laboratory Examinations.—The sputum showed untypable pneumococci. Blood counts were as follows: March 15, white blood cells 15,000 and polymorphonuclear cells 73 per cent; March 22, white blood cells 15,850 and polymorphonuclear cells 88 per cent; March 26, white blood cells 8,700. The urine was normal, and the Kahn reaction of the blood was negative. Roentgenograms of the chest on March 15 showed infiltration at the base of the left lung consistent with atypical pneumonia. Five days later there was infiltration on both sides with a small amount of fluid at the base of the left lung. In eleven more days the chest was normal.

Course.—The patient's temperature on admission was 102 F., and it dropped to normal the next day. It then rose daily from normal to 101 F. for seven days until March 20, when it rose to 103 to 105 F. for forty-eight hours. This last rise in temperature coincided with the appearance of pains in the joints and a generalized morbilliform eruption consistent with a drug eruption. Administration of sulfathiazole, which had been given in a dose of 6 Gm. daily since the patient's admission, was discontinued, and the fever, rash and arthralgia disappeared in two days. The physical signs became more pronounced during the first seven days, but by the eleventh day there remained only dulness and diminished bronchovesicular breath sounds at the base of the left lung. At that time the cough was minimal, and it disappeared shortly thereafter.

CASE 5.—A white man aged 22 was admitted to the hospital Nov. 12, 1942 and discharged Jan. 27, 1943.

History.—His past history was irrelevant. About two days before admission he noted chilliness, slight sore throat, frontal headache and a mild, nonproductive cough. The dizziness diminished, but the other symptoms progressed.

Physical Examination.—The patient was acutely ill. He was chilly and felt dizzy when upright. His lips were dry; his tongue was coated, and crusting was present around the nares. Left external strabismus was present. There was no nystagmus or stiffness of the neck. The blood pressure was 95 systolic and 65 diastolic.

Laboratory Examinations.—Lumbar puncture was done on November 14. The globulin was not increased; the fluid contained 5 lymphocytes per cubic millimeter; the colloidal gold curve was 1111000000; the Wassermann reaction was negative, and the protein content was 34 mg. per hundred cubic centimeters. Culture of material from the left ear on Jan. 18, 1943 yielded Staph. albus. Blood counts are shown in the table.

Roentgenograms of the Chest.—On November 13 a hazy infiltration consistent with atypical pneumonia and accumulation of the fluid was seen at the base of the

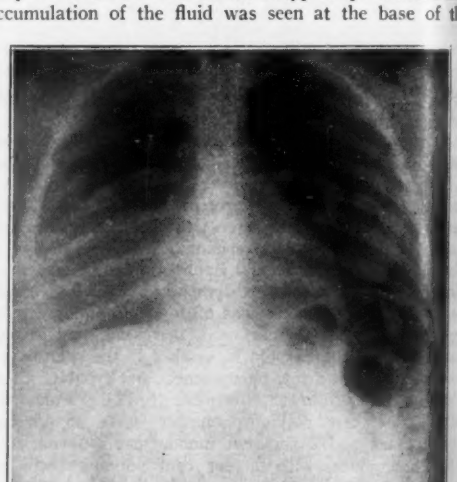

Fig. 2 (case 5).—Fluid at the base of the right lung nine days after the onset of the illness.

White Blood Cell Counts in Case 5

Date	White Cells	Mature Granulocytes, %	Stab Cells, %	Immature Granulocytes, %	Lymphocytes, %	Large Lymphocytes, %	Immature Lymphocytes, %
11/14	2,200	0	16	43	16	19	6
11/16	3,800	0	15	38	19	8	19
11/17	2,300	0	31	27	14	8	14
11/20	3,800	6	48	19	15	0	2
11/21	6,500	6	40	6	17	5	26
11/24	10,950	11	38	11	32	2	3
12/29	7,400	40	25	3	26	0	3
1/25	5,800	10	49	0	33	0	9

right lung. This increased in extent for one week (fig. 2) but began to clear two weeks after the onset. At the end of three weeks a small amount of fluid was present at the base of the right lung, but this was gone one week later. The entire chest was not clear until nine weeks after the onset.

Course.—The patient's temperature was normal on his admission but rose to 105 F. the next day. Thereafter there was a remittent fever with temperature from 100 to 105 F. until November 21, when the temperature dropped to normal. It stayed normal until December 10. During that period the following events occurred: On November 14 the vertigo had disappeared, the cough had increased and rales appeared at the base of the right lung. On that day the patient had a short period of stiffness of the neck with questionably positive Kernig and Brudzinski signs. A lumbar puncture was done; the pressure was 160 mm. and the fluid was clear. He complained of pleuritic pain in the right side of the chest and had diminished bronchovesicular breathing sounds at the base of the right lung and in the right anterior portion of the chest with rales in the latter area. On November 18, he had rales to the level of the sixth thoracic vertebra posteriorly on both sides, with bronchovesicular sounds over the same areas. The toxicity decreased, and he was mentally clearer. On November 24, the cough continued, and pleuritic pain returned, with a definite leathery rub in the lower part of the right axilla. On November 29, the rub was gone but pleuritic pain was still present. On December 10, the temperature rose to 101 F. It then had a remittent course from 99 to 104 F. through December 16, when it dropped by lysis, reaching a normal level by December 18. On December 10 the patient complained of pain in the right shoulder. During the next five days rales appeared in the right infraclavicular region, with bronchovesicular breath sounds and sibili, but these signs subsequently disappeared. On Jan. 9, 1943, his temperature suddenly rose to 103 F. for one day. On January 10, he complained of nasal discharge and sore throat. Physical examination showed follicular patches in the throat. During the next three days he complained of pain in both ears, and the left showed bullous inflammation of the tympanic membrane, which was incised with drainage of pus. Sulfathiazole was given from January 13 through January 22, during which time the discharge from the ear subsided.

This case illustrates an unusual complication of the hemopoietic system as well as pleural effusion. The white blood cell count rose on the day of defervescence, but the abnormal cells persisted longer. The patient was allowed to be up before the fluid was completely absorbed, and he promptly had a relapse, which was accompanied by spread to the upper lobe of the right lung without further hemopoietic complications.

CASE OF PNEUMONIA SIMULATING TUBERCULOSIS WITH DEVELOPMENT OF SPONTANEOUS PNEUMOTHORAX WHILE PATIENT WAS ASYMPTOMATIC

CASE 6.—A white man was admitted to the hospital July 9, 1943 and discharged July 29.

History.—The past history was irrelevant. The patient was admited because of mental depression and suicidal ideas, present for two or three weeks.

Physical Examination.—The patient seemed essentially normal.

Laboratory Findings.—The white blood cells numbered 8,900 per cubic millimeter, with polymorphonuclear leukocytes 72 per cent and lymphocytes 28 per cent. The hemoglobin content was 89 per cent. The urine was normal. The sedimentation rate (determined by the Wintrobe method) was normal. The sputum repeatedly failed to yield tubercle bacilli.

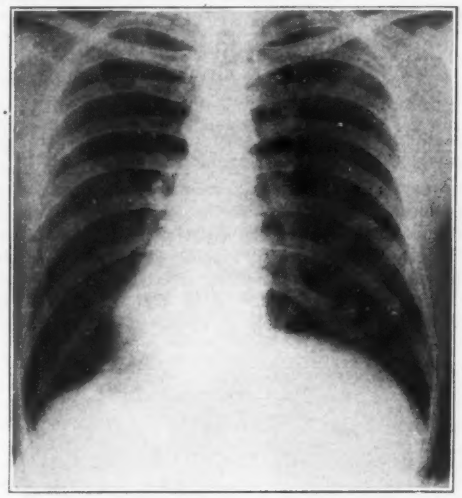

Fig. 3 (case 6).—Mottled infiltration in the right upper pulmonary field simulating tuberculosis.

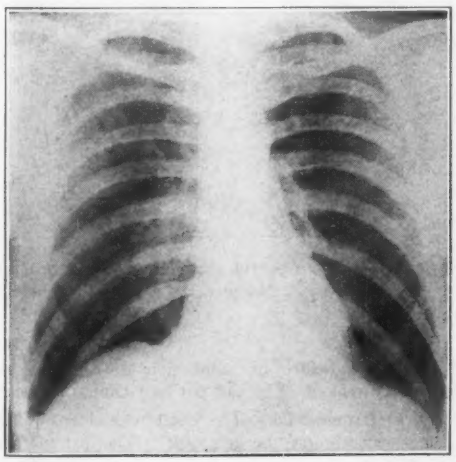

Fig. 4 (case 6).—Later film than that of figure 3, showing a small spontaneous pneumothorax at the apex of the right lung.

Progress.—The temperature was normal on the patient's admission but peaked to 99 F. on the first two afternoons. It was subsequently normal when the patient was kept at rest in bed. No cough was observed during his hospitalization. A diagnosis of manic-depressive psychosis was made, and he was transferred to another institution.

Roentgenograms of Chest.—Of greatest interest were the roentgenograms of the chest. The one on July 23 (fig. 3) showed a soft cottony infiltration in the right in-

fraclavicular region extending out into the first interspace from the hilus. Subsequent roentgenograms, made after the patient's discharge to another hospital, showed (fig. 4) complete clearing of the infiltration, but a small apical pneumothorax had appeared, extending down as far as the first and second interspaces.

THREE CASES OF APUTRID PULMONARY ABSCESS WHICH RESOLVED PROMPTLY AND ONE CASE OF SECONDARY INFECTION WITH PULMONARY ABSCESS, EMPYEMA AND DEATH WITH AUTOPSY

CASE 7.—A white man aged 29 was admitted to the hospital on Jan. 11, 1943 and discharged March 10.

History.—The patient had been a stone cutter. For two weeks before admission he suffered from cough associated with pain in the right side of the chest at the region of the right nipple. Five days before admission he was confined to quarters with a temperature of 100.2 F., mostly in the afternoon. He had been raising a couple of spoons of sputum daily,

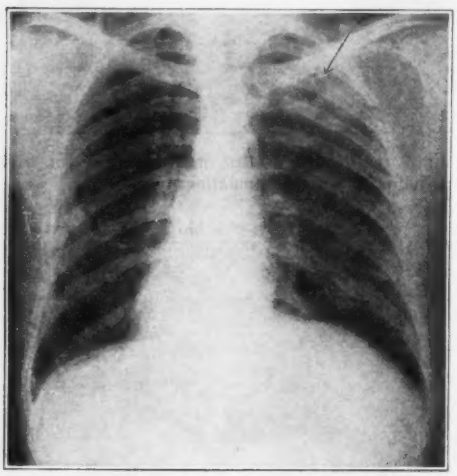

Fig. 5 (case 7).—Aputrid abscess cavity in the right upper pulmonary field nineteen days after the onset of cough.

and four days before his admission the sputum had been blood streaked. He had not had chills or sweats.

Physical Examination.—The chest was clear. There was a varicocele on the left side. The patient was not acutely ill.

Laboratory Examinations.—The sedimentation rate on February 19 was 0.3 mm. On January 12 there were 9,250 white cells. On February 23 the red cells numbered 5,000,000. There was no subsequent leukocytosis. Five three-day concentrates of the sputum for tubercle bacilli failed to reveal any. On February 2 a heavy growth of viridans streptococci was obtained; on February 9, hemolytic staphylococci, gram-negative diplococci and nonhemolytic streptococci. On January 9 the gastric washings failed to reveal tubercle bacilli on smear. A culture of material from the throat taken January 30 yielded nonhemolytic streptococci and gram-negative diplococci. The urine and the Kahn reaction of the blood were negative.

Roentgenograms of the Chest.—On January 9 there was a hazy infiltration in the upper lobe of the right lung which was consistent with atypical pneumonia. One week later an area of rarefaction was present in the center of that area, and this was thought to represent an abscess (fig. 5). The area of infiltration and the abscess rapidly resolved, and in about one month the chest was clear.

Course.—From January 11 through January 14, the temperature varied from normal to 99.6 F. On January 15 it suddenly rose to 102.6 F., but it came down to 99 F. by January 19. Then it fluctuated from normal to 100 F. through February 3, when it returned to normal. It stayed normal until February 11, and then fluctuated between 97 and 99 F. daily throughout the remainder of the course. No abnormal physical signs were found at any time. A tuberculin test done on February 13 with 0.01 mg. of old tuberculin elicited a negative reaction, a test on February 15, with 0.1 mg. gave a positive reaction. The patient brought up only a small amount of sputum, never especially purulent or foul.

CASE 8.—A white man aged 25 was admitted to the hospital April 9, 1943 and discharged May 4.

History.—He had had pneumonia when he was 19. One week before admission he had noted onset of headache, malaise and chill. This was followed by a running nose, slight sore throat and a dry cough, which soon became productive of white phlegm. For three days before admission he had had hoarseness. The headache persisted up to his admission, although the nasal discharge had disappeared.

Physical Examination.—The patient had a slight nasal discharge. There was no dulness or altered breath sounds, but there were sibilant and moist rales anteriorly from the right clavicle down to the fifth rib and laterally to the anterior axillary line. The blood pressure was 105 systolic and 65 diastolic.

Laboratory Examinations.—The sputum on April 20 failed to show tubercle bacilli by smear or on inoculation of a guinea pig. The sedimentation rate of the blood on April 30 was 0.4 per minute. Blood counts were as follows: April 9, white cells 24,500, with polymorphonuclear cells 79 per cent; April 13, white blood cells 13,150; April 28, white blood cells 7,700, with polymorphonuclear cells 68. The urine was normal. The Kahn reaction of the blood was negative.

Roentgenograms of the Chest.—On April 10, roentgen examination showed a large area of infiltration involving the hilar zone and the lower portion of the upper lobe of the right lung, which was thought to be pneumonia. Five days later an area of rarefaction consistent with abscess appeared in the same lobe. Twelve days later, or seventeen days after the first film was made, the lung showed almost complete clearing.

Course.—The temperature, which was 100.2 F. on the patient's admission, rose to 104.8 F. the same day and then gradually came down to normal in eight days. On the eighth day, administration of sulfadiazine was started because of roentgen findings of pulmonary abscess; 6 Gm. daily was given through the tenth day and 4 Gm. a day from the eleventh through the twentieth day, a total of 58 Gm. On April 11, there were medium moist rales over the entire upper lobe of the right lung. On April 16, only a few post-tussive rales were heard just lateral to the right third and fourth costochondral junctures. On April 18, the cough had diminished, although the patient was bring-

ing up small amounts of nonfoul green sputum. Throughout his stay he had a complaint of a constant aching pain in the right upper quadrant of the chest, which disappeared, along with the cough, by April 19.

CASE 9.—A white man aged 38 was admitted to the hospital Dec. 15, 1942 and discharged Jan. 19, 1943.

History.—His past history was irrelevant. For two days he had suffered from chilly feelings, running nose, cough, occipital headache and a few mild aches in the legs. Sore throat had been present for twelve hours.

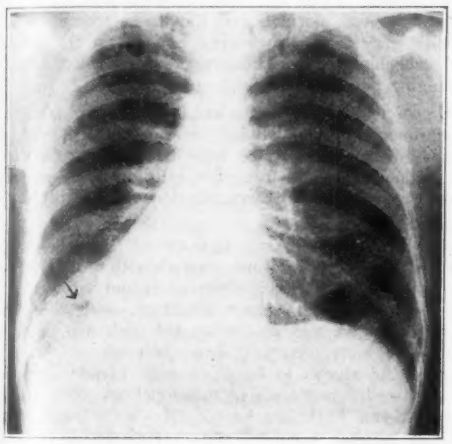

Fig. 6 (case 9).—Aputrid abscess at the base of the left lung sixteen days after the onset of cough. Note the fluid level.

Physical Examination.—The pharynx was diffusely red, the tonsillar lymph nodes were enlarged. There were a few coarse rales at the base of the left lung.

Laboratory Examinations.—Blood counts were as follows: December 15, white cells 7,000, with 74 per cent polymorphonuclear cells; December 21, white blood cells 15,000; January 12, white blood cells 9,000; January 22, white blood cells 8,000. The urine was normal.

Roentgenograms of the Chest.—On December 16 the roentgenogram was normal. Seven days later there was a dense infiltration at the base of the left lung. Six days after this an area of rarefaction appeared in the same location, which was thought to represent an abscess (fig. 6). The base of the lung gradually cleared, but the abscess remained for two weeks. At the end of another month, the chest had cleared entirely.

Course.—The temperature on the patient's admission was 101.6 F. It came down to normal by lysis by December 19. It rose abruptly to 104 F. on December 20 and came down remittently by lysis to normal on January 1. The respiratory rate was never above 24. Administration of sulfadiazine was started on December 31 and continued through January 12. The rales heard on admission disappeared, but on January 2 reappeared at the base of the right lung. On January 15, in spite of positive roentgen findings, physical examination revealed nothing significant. The patient generally had a mild cough, and he felt poorly only from December 21 through January 2. On the latter date he felt much better and there was very little cough remaining. Sputum was minimal and mucoid.

CASE 10.—A white man aged 30 was admitted to the hospital Dec. 4, 1942 and died Jan. 16, 1943.

History.—The family and the past history were irrelevant. For three days the patient had had fever, with temperature up to 103 F., malaise, backache, chilly sensations and mild, nonproductive cough.

Physical Examination.—The patient was uncomfortable but not acutely ill. He had an occasional dry cough, and his skin was flushed. The conjunctivas were injected. The throat was slightly inflamed. The lungs were normal. The pressure was 106 systolic and 70 diastolic.

Laboratory Examinations. — An electrocardiogram taken on January 11 showed a rate of 111, a PR interval of 0.14 second, slight deviation of the axis to the right, and a diphasic T wave in lead III. The interpretation was: beginning deviation of the axis to the right, probably associated with subacute pulmonary disease. Cultures of material from the throat revealed the following organisms: December 5, staphylococci and gram-negative diplococci; December 7, untyped pneumococci; December 10, hemolytic and nonhemolytic streptococci; January 15 and 19, hemolytic streptococci and Staphylococcus albus. Cultures of blood revealed: January 19, gram-negative diplococci and streptococci; post mortem, January 30, pure growth of hemolytic streptococci. Culture of material from the lungs showed: January 30, left lung, pure growth of hemolytic streptococci, and right lung streptococci and Staph. aureus haemolyticus. Blood counts were as follows: December 4, white cells 8,900, with 74 per cent polymorphonuclear cells; December 14, white cells 11,000, with polymorphonuclears 78 per cent; December 22, white cells 13,000, with polymorphonuclears 91 per cent; December 26, white cells 14,500, with polymorphonuclears 89 per cent; January 1, white cells

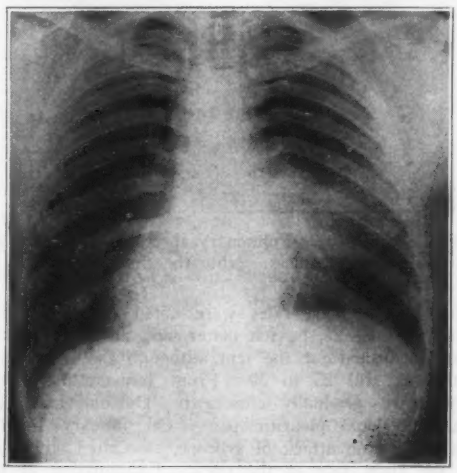

Fig. 7 (case 10).—Infiltration of the right pulmonary field five days after the onset of severe primary atypical pneumonia.

20,000, with polymorphonuclears 82 per cent; January 5, white cells 25,000; January 12, white cells 27,000, with polymorphonuclears 92 per cent; January 14, white cells 30,000, with polymorphonuclears 93 per cent. The urine was normal, and the Kahn reaction of the blood was negative.

Roentgenograms of the Chest.—On December 6, a light hazy area was seen in the right hilar zone (fig. 7).

This increased rapidly in size, and in about a week the entire right lung was involved, together with the upper lobe and the base of the left lung. The fine splotchy infiltration involving both lungs cleared somewhat at times, but about 60 per cent of both lungs remained involved for about a month. At this time, which was six weeks from the onset, an abscess developed at the apex of the right lung (fig. 8). The major portion of both lungs still showed a dense stringy infiltration throughout.

Course.—The temperature on the patient's admission was 103 F. It fluctuated remittently from 99 to 105 F. through December 11 and then gradually dropped by lysis to 99 F. on January 12, when it rose to 102 F. abruptly. Thereafter it ran from 99 to 104 F. until the patient's death, January 16. On December 6, the patient complained of headache and dulness and rales were noted at the base of the right lung. On December 10, the respiratory rate, which had been 20 to 25, rose suddenly to 32. On December 11, the cough was more productive, the sputum was mucopurulent, there was only slight cyanosis, and the spleen was palpable 2 fingerbreadths below the costal margin. On December 15, the cyanosis was worse, and breathing was labored. On December 25, the patient was placed in an oxygen

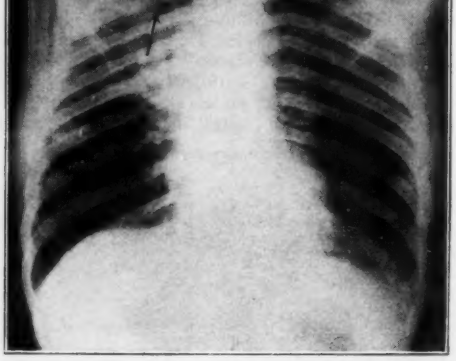

Fig. 8 (case 10).—Pulmonary abscess six weeks from the onset of the illness. Note the fluid level.

tent; coarse moist rales were noted over his chest. On December 28, he felt better, and an oxygen mask was substituted for the tent, although the respiratory rate was still 25 to 30. From January 6 on, the oxygen was gradually withdrawn. The only complaint was occasional pleuritic pain. On January 11, the patient had an attack of syncope, associated with pain in the right side of the chest. Examination of the chest revealed nothing abnormal. An electrocardiogram was taken January 14 (see report of laboratory examinations). On January 15, the patient appeared worse, his appetite was poor, he felt pain in the left side of the chest, and there were rales at the bases of both lungs and in the right axilla. On January 16, the patient declined rapidly, became pulseless, brought up much frothy sputum and died. Sulfadiazine was administered from December 5 through December 12, but this treatment was stopped because of red blood cells and casts in the urine. After clearing of urine the drug was readministered from December 17 through December 22.

Gross Observations at Autopsy.—Thoracic Cavity: There were numerous fine adhesions all over the right lung and at the base of the left lung. The right lung weighed 1,025 Gm.; on section, the upper lobe was firm and yellowish to pink gray and the lower lobe was nodular with yellow purulent exudate in the larger bronchi and the dilated bronchioles. In the upper lobe near the apex an abscess cavity 4 by 3 by 2 cm. was found; it contained thick yellow purulent exudate and its walls were covered with a shaggy yellow-gray layer of fibrin and necrotic tissue. No direct connection between this cavity and the smaller bronchi could be demonstrated. The left lung weighed 755 Gm. The upper lobe was normal, and the lower lobe was dark reddish gray with yellow-gray exudate in the bronchi and bronchioles. The hilar nodes bilaterally revealed a bulging, succulent, pinkish gray surface.

Microscopic Observations at Autopsy.—Bronchus and Peribronchial Lymph Node: Section revealed moderate edema of the lymph node with increased proliferation of mononuclear and reticular cells in the sinusoids. There were also rare accumulations of neutrophils in the sinusoids.

Right Lung: Several sections of the right lung revealed the pleura to be covered with a thick layer of fibrin containing many neutrophils and a few macrophages. The pleura was edematous, with the capillaries engorged, and was infiltrated with many neutrophils and macrophages. Some sections of the slide showed the alveoli to be filled with variable numbers of red cells, neutrophils, mononuclears and macrophages in a fibrin meshwork. In some regions the cellular exudate consisted almost entirely of red cells and neutrophils, while in others mononuclears and lipid-laden macrophages predominated. The alveolar walls were swollen and infiltrated with mononuclears. In other areas the cellular exudate showed beginning organization with ingrowth of capillaries and fibroblasts. The wall of the abscess cavity, noted on gross examination, consisted of a layer of fibrin and degenerating exudate overlying a wall of juvenile connective tissue and budding capillaries which in turn was heavily infiltrated with mononuclears, lipid-laden macrophages, plasma cells and occasional neutrophils and foreign body type giant cells. Besides this large abscess cavity there were many small abscesses consisting of large focal accumulations of neutrophils with destruction of all intervening alveolar walls. Left lung: The pleura was essentially normal. The bronchioles contained a fibrinous exudate in which were desquamated epithelium and many neutrophils and mononuclears. Their walls were edematous and infiltrated with many mononuclears and neutrophils and occasional foreign body type giant cell. One bronchiole showed beginning organization of its fibrinous exudate by ingrowth of capillaries and juvenile connective tissue. Many of the peribronchial alveoli showed a hemorrhagic infiltration. Other alveoli contained edema fluid, and variable numbers of red cells, neutrophils and macrophages in a fibrin meshwork. In other regions lipid-laden macrophages replaced the red cells and neutrophils. Occasional small areas were found in which the exudate showed signs of organization.

In analyzing the course of these patients with pulmonary abscess, it was seen that this complication occurred on the nineteenth, the thirteenth, the sixteenth and the forty-second day of their respective illnesses. In additional cases of atypical pneumonia without abscess formation it

was noted that the leukopenia present on the patients' admission was succeeded by a moderate leukocytosis (15,000 to 18,000 white cells) during the afebrile period of the convalescence, about the eighteenth day. Sometimes this was associated with an increased amount of sputum.

TWO CASES ILLUSTRATING OCCURRENCE OF FEVER, LEUKOCYTOSIS, SPREAD OF THE PNEUMONIA AND PROMPT RESPONSE TO TREATMENT WITH SULFONAMIDE COMPOUNDS DURING CONVALESCENT STAGE OF THE DISEASE

CASE 11.—A white man aged 21 was admitted to the hospital on June 30, 1943 and discharged July 26.

History.—His family and his past history were irrelevant. For four days he had had nonproductive cough, feverishness, severe postorbital headache and temperature as high as 101 F.

Examination.—Physical examination revealed a dry, coated tongue and dulness, bronchial breath sounds and bronchophony at the base of the right lung.

Examination of the sputum on June 30 and July 14 failed to reveal pneumococci. Leukocyte counts were as follows: June 30, 14,300 with 80 per cent polymorphonuclear cells; July 1, 8,900, with 73 per cent polymorphonuclear cells; July 10, 21,550; July 12, 18,500 with 85 per cent polymorphonuclear cells; July 14, 13,800; July 17, 7,400.

Roentgenograms of the chest revealed the following significant features: June 30, a dense hazy area at the base of the right lung; July 5, the area of haziness more extensive, with a small amount of fluid present; July 12, 50 per cent clearing of the base of the right lung and a small area of infiltration at the base of the left lung; July 17, all abnormalities diminishing; July 23, complete clearing.

Course.—The cough, distressing at the onset, gradually subsided. The initial temperature of 101 F. dropped to normal on the fifth day of the patient's hospitalization (eighth day of the illness), but there was another rise to 99 to 101 F. during the tenth to fifteenth day of the hospitalization (fourteenth to nineteenth day of the illness), coincidental with the rise of the white blood cell count to 21,550 on July 10. These changes were unaccompanied by increase in the cough.

This case illustrated a spread of the infection on the tenth day of the patient's hospitalization (fourteenth day of the illness), accompanied by definite leukocytosis, probably indicative of invasion by secondary organisms, in contrast to the lack of leukocytosis at the onset.

CASE 12.—A white man aged 24 was admitted to the hospital on Nov. 24, 1942 and discharged on December 27.

History.—The family and past history were irrelevant. For two days the patient had had cough, productive of yellow sputum, pain in the right shoulder and fever.

Examination.—Physical examination revealed a slightly inflamed pharynx and bronchovesicular breath sounds posteriorly over the left side of the chest at the level of the fifth to eighth thoracic vertebrae.

Blood culture on December 13 gave negative results. Leukocyte counts were as follows: November 25, 7,900; December 13, 21,600, with 91 per cent polymorphonuclears; December 19, 8,100. Culture of the sputum on November 26 revealed gram-negative diplococci; smear failed to reveal pneumococci; on December 8, a smear did not show any tubercle bacilli. Roentgenograms of the chest on November 25 showed a dense infiltration in the medial third of the left lung extending out from the hilus; on December 12, slight residual infiltration was still present.

Course.—The cough and sputum increased for several days after the patient's admission to the hospital, and rales spread all over the lower half of the left side of the chest posteriorly. Simultaneously with the drop in temperature during the first eleven days of the hospitalization (thirteen days of the illness), the cough and physical signs began to clear. On December 13, (eighteenth day of hospitalization or twentieth of illness), he had a chill and a rise of temperature, together with return of cough and purulent sputum and signs of consolidation at the base of the right lung. All the signs and symptoms cleared rapidly in three days under sulfadiazine therapy.

This case illustrated again a spread of pulmonary infection late in the convalescence, accompanied by leukocytosis.

COMMENT

In many respects the complaints referable to the central nervous system that have been noted, e. g. stiffness of the neck, headache, disorientation, vertigo and strabismus, make one think of pneumonia in children, since these symptoms rarely usher in an attack in adults. Cunningham [3] reported such symptoms in 8 per cent of 1,500 children with pneumonia. Adams and Berger [4] stated that 4.8 per cent of 145 children with pneumonia were admitted to the hospital with a diagnosis of meningitis. However, involvement of the central nervous system such as was evident in cases 1, 2 and 5 has been previously noted by others [5] in atypical pneumonia, though details were not always given. Reimann [5a] mentioned 5 such cases, in 1 of which (case X) there was a spinal fluid cell count of 350, of which 75 per cent were polymorphonuclears, and the total protein measured 74 mg. per hundred centimeters. Kneeland [5c] reported 1 patient (out of 52 with atypical pneumonia) with stiff neck and stupor

3. Cunningham, A. R.: Results of Open Air Treatment of Pneumonia in Children: An Analysis of 1,500 Cases of Lobar Pneumonia from the Records of the Children's Hospital, Boston, Boston M. & S. J. **174**: 753 (May 25) 1916.

4. Adams, F. D., and Berger, B. J.: Differential Diagnosis of Lobar Pneumonia and Appendicitis in Children, J. A. M. A. **79**:1809 (Nov. 25) 1922.

5. (*a*) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia, J. A. M. A. **111**:2377 (Dec. 24) 1938. (*b*) Gallagher, J. R.: Acute Pneumonitis: A Report of Eighty-Seven Cases Among Adolescents, Yale J. Biol. & Med. **13**:663 (May) 1941. (*c*) Kneeland, Y., Jr., and Smetena, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**:229 (Oct.) 1940. (*d*) Allen, W. H.: Acute Pneumonitis, Ann. Int. Med. **10**:441 (Oct.) 1936.

whose spinal fluid contained only 4 cells. It is important to bear in mind that stupor, stiff neck and disorientation may occasionally dominate the clinical picture of this disease at the onset, especially in view of the paucity of physical signs of the pulmonary involvement that so often exists during the first week.

Small amounts of pleural fluid have been mentioned in other reports. For example, Smiley and associates,[6] in a report of 86 cases, said that "in about 5 per cent of the cases the involvement was severe. . . . In this group there was a decided tendency to some involvement of the interlobar pleura and, in one case, of the parietal pleura." In a report of 132 cases of pneumonia in college students Murray [7] found 1 case with "x-ray evidence of questionable fluid." Our patients with fluid (cases 3, 4, 5 and 10) were all moderately or severely ill. In all of them the fluid absorbed slowly without tapping the chest. We did notice a tendency to relapse or spread of the parenchymal infection in the patients with pleural involvement, especially when they were allowed to become ambulatory too soon. Case 5, with the leukopenia and marked outpouring of immature cells, seems to be unique, for no such complication has been previously reported. Prompt return of the blood picture to normal coincided with defervescence. It is interesting that the patient did have a mild leukocytosis with the late secondary infection of his throat and ear and that sulfathiazole was used at that time without adverse effect on his blood.

The 3 cases with aputrid pulmonary abscess (cases 7, 8 and 9) are similarly unlike those reported elsewhere. The resemblance of the condition to tuberculous cavitation, especially when located in the upper pulmonary fields, is noteworthy, but such a cause was ruled out in our cases by the clinical course and laboratory studies. The pathogenesis seems to be that of infection by secondary invaders during the convalescent period of the disease. Examples of such invasion of the throat (case 1) and the middle ear (case 2) as well as the lungs without abscess formation (cases 11 and 12) are given. Such superinfections are accompanied by leukocytosis, in contradistinction to the primary disease. Moreover, the use of sulfonamide compounds at such times has the same therapeutic effectiveness as with primary bacterial infections, whereas their ineffectiveness in primary atypical pneumonia is now well recognized. Finally, it cannot be overemphasized that if such aputrid abscesses are encountered in the future, the benign course in our cases should be borne in mind and surgical intervention should certainly be withheld in favor of conservative therapy.

Our 1 fatality was in a case (case 10) of primary atypical pneumonia of great severity and superimposed secondary infection at a time when the patient was debilitated though recovering from the primary disease. This is the type of situation that occurs frequently in debilitating chronic disease of all kinds; however, it has been noted in primary atypical pneumonia previously,[8] with empyema, pulmonary abscess and extension of the pneumonia after invasion by streptococci or staphylococci. The incidence of such a severe complication is extremely low in this disease. In fact, Kneeland and Smetana [8e] said of secondary bacterial infection: "Our clinical impression was that secondary bacterial infection of the lungs occurred so rarely as to make it seem that the disease might actually predispose against it." It does not seem justified to advocate the routine use of full doses of sulfonamide compounds from the onset of treatment of atypical pneumonia in order to prevent the aforementioned late complications, since complications due to these drugs are more frequent and more dangerous than secondary bacterial complications.

If it is considered worth while to attempt to prevent late secondary bacterial complications, it is suggested that the drug should be given after the first week and in relatively small, nontoxic doses, such as 3 Gm. per day for adults.

SUMMARY

Of 180 cases of all varieties of pneumonia reported in a nine month period among soldiers, 150 were classified as instances of primary atypical pneumonia.

Complications noted were 3 instances of meningismus, 3 of pleural effusion, 1 of extreme leukopenia, 1 of spontaneous pneumothorax, 1 of benign pulmonary lung abscess and 1 of fatal pulmonary abscess and empyema among 10 patients.

An attempt was made to elucidate the pathogenesis and treatment of the pulmonary abscesses occurring during the course of primary atypical pneumonia.

6. Smiley, D. F.; Showacre, E. C.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901 (May 13) 1939.

7. Murray, M. E., Jr.: Atypical Bronchopneumonia of Unknown Etiology, Possibly Due to a Filterable Virus. New England J. Med. **222**:565 (April 4) 1940.

8. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, J. Pediat. **20**:405 (April) 1942. McKinlay, C. A., and Cowan, D. W.: Acute Respiratory Infections, Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group, Journal Lancet **61**:125 (April) 1941.

EFFECT OF PROLONGED PHYSICAL INACTIVITY ON TOLERANCE OF SUGAR

HARRY BLOTNER, M.D.
BOSTON

It is recognized that exercise increases the utilization of dextrose. This fact was first demonstrated by Rakestraw [1] and by Levine [2] and their associates, who observed in normal people that a long period of exercise is usually accompanied by a drop in the level of sugar in the blood, although short, strenuous exercise increases the concentration of sugar in the blood. Exercise also lowers the level of blood sugar of persons with diabetes who have an adequate supply of insulin. This effect is so striking that exercise [3] is now accorded a prominent place in the treatment of diabetes along with diet and insulin. In contrast, there has been no work to show the effect of physical inactivity or prolonged rest in bed on the carbohydrate metabolism in nondiabetic persons. The fact that exercise increases the carbohydrate metabolism does not necessarily mean that inactivity will do the opposite. If such reasoning were followed one would expect to find an improved carbohydrate tolerance in normal thin persons taking insulin to gain weight. However, this is not the case, since in a large number of these persons a diminished sugar tolerance has been found [4] during the period of treatment with insulin.

It seemed of practical interest to study this problem by observing whether the carbohydrate metabolism was disturbed in a group of nondiabetic patients who had been confined to bed for relatively long periods of time. This would appear to be of particular importance now, since many persons injured in the war will be confined to bed for considerable periods and the problem of interpreting values for sugar tolerance for some of them will undoubtedly arise.

This paper reports the results of dextrose tolerance tests obtained in 86 nondiabetic persons —70 adults and 16 children—who had been long in bed because of certain diseases.

PLAN OF INVESTIGATION

Since the simplest test available at present to determine the integrity of the mechanism of carbohydrate metabolism is that for dextrose tolerance, this test was used. The values for dextrose tolerance of patients who had been in bed in the hospital from four weeks to eight years were compared with observations made on 10 normally active adults and on 11 active children. A standard dose of 100 Gm. of dextrose was used for the adults. The dose was 50 Gm. for a child who weighed less than 75 pounds (34 Kg.) and 75 Gm. for one who weighed more than 75 pounds. The dextrose was mixed with 250 cc. of water, flavored with 50 cc. of lemon juice, chilled and ingested after the patient had fasted overnight. The concentration of sugar in the blood and in the urine was determined in specimens taken during fasting and at intervals of one-half hour and one, two and three hours after the ingestion of the dextrose mixture. The determinations [5] of the blood sugar were made in all cases on 0.1 cc. samples of capillary blood according to the micromethod of Folin and Malmros.[6] Simultaneous determinations of capillary and of venous blood sugar were made for all of the children and for 18 inactive and 10 active adults in order to study the arteriovenous differences in the blood sugar. The capillary and venous bloods were obtained by two operators simultaneously from the antecubital veins and from the finger tips. The venous blood was mixed with powdered sodium oxalate, and then immediately 0.1 cc. of this blood was treated like capillary blood.

The test for sugar in the urine was made with Benedict's solution. In 24 cases the sugar tolerance tests were repeated under the same conditions, on one

Nearly all of the adults were studied at the Jewish Memorial Hospital, where Dr. Rudolph Haas and Dr. Israel R. Duke assisted. The children were studied at the New England Peabody Home for Crippled Children through the courtesy of Dr. Frank R. Ober and Dr. Gerald N. Hoeffel, Boston.

1. Rakestraw, N. W.: The Effect of Muscular Exercise upon Certain Common Blood Constituents, J. Biol. Chem. **47**:565, 1921. Rakestraw, N. W.; Barley, C. V., and Hahn, Y. D.: Further Changes in Some of the Blood Constituents Following Strenuous Muscular Exercise, ibid. **56**:121, 1923.

2. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race with Special Reference to the Development of Hypoglycemia, J. A. M. A. **82**:1778 (May 31) 1924. Gordon, B.; Kohn, L. A.; Levine, S. A.; Matton, M.; Scriver, W. M., and Whiting, W. B.: Sugar Content of the Blood in Runners Following a Marathon Race, ibid. **85**:508 (Aug. 15) 1925.

3. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 333.

4. Blotner, H.: Insulin and Sugar Tolerance in Thin People, Arch. Int. Med. **53**:153 (Jan) 1934.

5. Miss Muriel Reiner gave technical assistance.

6. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115, 1929.

to three occasions after varying intervals to see whether there would be any changes in the results. In 10 cases the sugar tolerance tests were made after the formerly bedridden patients had been ambulatory for two to six months.

When it was found that so many of the adult inactive patients had a diminished sugar tolerance and that age may have been a factor in these results, the sugar tolerance of a group of 16 inactive children was studied.

CLINICAL MATERIAL

There were studied first 70 consecutive nondiabetic patients, 36 men and 34 women. Most of the patients were of normal or slightly below normal weight for their height, age and sex. The weight of a few patients was above or below normal. The 4 heaviest patients weighed 175 pounds (79 Kg.) each. Nearly all of these patients and those of the control group were Jewish. Their ages varied from 18 to 92 years, as follows: Seven patients were from 18 to 41 years old; 12, from 41 to 51 years; 16 from 51 to 61 years; 21, from 61 to 71 years, and 12, from 71 to 78 years; 2 were 80 and 92 years old respectively.

The patients received the routine house diet, which consisted of approximately 250 Gm. of carbohydrate, 70 Gm. of protein and 75 Gm. of fat. The daily intake was approximately 2,000 calories, with an adequate amount of protective foods. The adults had various pathologic conditions, such as hereditary ataxia, polycythemia, tuberculous spondylitis, amyotonia atrophica, progressive muscular dystrophy, syringomyelia, the tabetic form of dementia paralytica, progressive muscular atrophy, multiple sclerosis, old cerebral hemorrhage, hemiplegia, atrophic arthritis, chronic myocarditis, coronary occlusion, hypertension, carcinoma of the bowel, bronchiectasis, fractured leg or hip, peptic ulcer, periarteritis nodosa, gout, lymphoblastoma, Parkinson's disease, amputation of both legs or of one leg, chronic colitis, and cancer of the lung or prostate. A moderate hypertension, with the blood pressure about 185 systolic and 95 diastolic, was present in 12 cases.

Practically all of these patients had been in bed for a considerable time before admission to the hospital. Before the sugar tolerance tests were made the patients had been confined to bed in the hospital as follows: 22 patients from one to four months, 20 from five to ten months, 21 from one to four years, 5 from five to seven years and 2 for eight years.

The children, all gentiles, had been confined to bed from seven months to thirteen years. There were 10 boys and 6 girls, their ages ranging from 4 to 13 years. Most of them were in casts or on traction. They had such conditions as tuberculosis of the spine and knee, Legg's disease, scoliosis, coxa vara, clubbed foot, inflammation of the hip, necrosis of the femur, old poliomyelitis, arthritis and progressive muscular dystrophy. They ate well and took a good general diet. Only 2 of the children appeared considerably overweight for their height.

In view of the results of the sugar tolerance tests, careful family histories with regard to diabetes were taken in all of the cases. It is interesting to note that a family history of diabetes was obtained for only 2 adult patients (3 per cent of the total number); each of these patients had 2 brothers with diabetes. None of the children had a history of diabetes in the family. This familial incidence of diabetes of 3 per cent is less than that found by Blotner and Hyde[7] for consecutive volunteers and selectees, 5.2 per cent of whom had a family history of diabetes.

RESULTS IN ADULTS

The results obtained in the adults and in the children are shown in the accompanying charts.

The criteria for interpreting the normal sugar tolerance are rather difficult to fix, because of the variable blood sugar curves which have been reported for so-called nondiabetic persons and consequently labeled normoglycemic curves. One of the best papers on the criteria for determining the normal sugar tolerance was written by Gray,[8] who studied 300 apparently healthy persons. His data showed the average normal fasting blood sugar to be 0.09 per cent and the average postprandial values to be 0.14 per cent in one-half hour, 0.12 per cent in one hour, 0.11 per cent in two hours and 0.09 per cent in three hours. These values remained the same after the ingestion of 50 to 100 Gm. of dextrose. Others have reported higher values for normal sugar tolerance curves, which may have been obtained from patients with chronic diseases.

In general, there was a diminished sugar tolerance in the patients who had been confined to bed for considerable periods. Of the 70 adults, 63 had definitely diminished sugar tolerance curves. Typical examples of the results of these curves tests are shown in chart 1. The fasting blood sugar ranged from 70 to 130 mg. per hundred cubic centimeters: in 37 cases it was from 70 to 105 mg., in 20 from 106 to 124 mg. and in 6 approximately 130 mg.

One hour after the ingestion of dextrose the blood sugar rose to abnormal levels, the maximum being 364 mg. per hundred cubic centimeters. At this time 34 patients had concentrations of blood sugar ranging from 180 to 225 mg., 22 had approximately 250 mg. and 7 had 290 to 364 mg. In two hours the levels of blood sugar decreased appreciably in some cases, and in a few they increased. In three hours 16 patients had levels of blood sugar of 120 mg. or less, and 47 had levels ranging from 140 to 278 mg. In all of these cases the specimens of fasting urine contained no sugar. After the ingestion of dextrose considerable amounts of

7. Blotner, H., and Hyde, R. W.: Renal Glycosuria in Selectees and Volunteers, J. A. M. A. **122**:432 (June 12) 1943; Studies in Diabetes Mellitus and Transient Glycosuria in Selectees and Volunteers, New England J. Med. **229**:885 (Dec. 9) 1943.

8. Gray, H.: Blood Sugar Standards: I. Normal and Diabetic Persons, Arch. Int. Med. **31**:241 (Feb.) 1923.

sugar, varying from 1 + to 4 +, were found often in the urine. However, it was quite striking to find that frequently the urine was free from sugar when simultaneous levels of blood sugar were 200 or 250 mg. This condition was found on repeated occasions even for the same persons. Apparently there was a high renal threshold for sugar in these cases. Often the patients who were in bed for the longest periods had the highest blood sugar curves. Some of the patients who were more active in their life

RESULTS IN CHILDREN

The results of sugar tolerance tests of 16 inactive children were of unusual interest because here too the tolerance was diminished, particularly as compared with the results obtained for the 11 normally active gentile children. However, the children's sugar tolerance curves did not rise as high as those of the adults. Typical examples of the sugar tolerance curves obtained for children are shown in chart 3. The fasting levels of blood sugar of the children

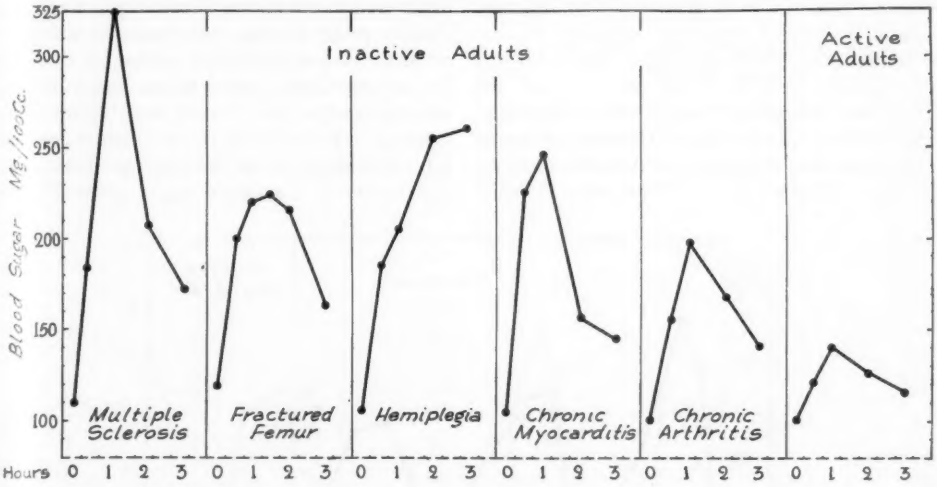

Chart 1.—Illustrations of blood sugar curves following the ingestion of 100 Gm. of dextrose for 63 nondiabetic adults with various diseases who had been confined to bed from one month to eight years.

in bed or in chairs did not have as greatly elevated blood sugar curves as those who were more restricted in activity. These rules, however, were not invariable. Hypertension, infection, arteriosclerosis and obesity in themselves did not appear to be significant in bringing about these results.

The age and sex did not appear to have any definite bearing on the dextrose tolerance in these cases, because a number of the patients between 18 and 50 years of age had abnormal results of the tests, whereas 10 active persons aged 53 to 73 had normal results. One arthritic patient aged 67 years who had been in bed for seven years had a normal sugar tolerance. In most cases in which sugar tolerance tests were repeated on several occasions under similar conditions there was almost no variation in the results.

For 10 patients who had been confined to bed for long periods sugar tolerance tests were repeated after they had been ambulatory from two to six months. The blood sugar was found to be normal in 6 cases, somewhat improved, although still abnormal, in 2 cases, and unchanged in 2 cases (chart 2).

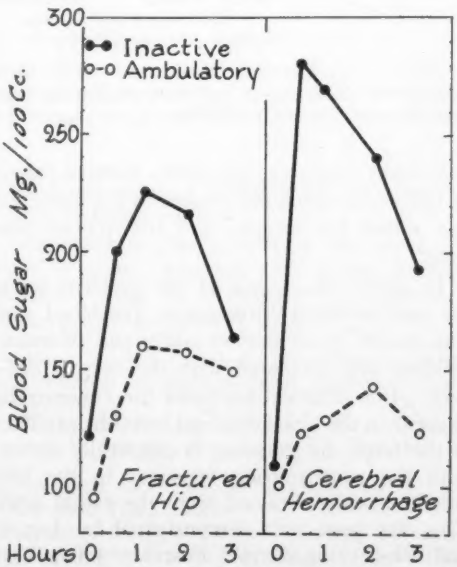

Chart 2.—Comparison of results of sugar tolerance tests of some patients when they were confined to bed and after they had been ambulatory for several months.

ranged from 90 to 107 mg. per hundred cubic centimeters. The greatest rise in the blood sugar one hour after the ingestion of dextrose was to 238 mg., which decreased to approximately 140 to 172 mg. in two hours and to 90 to 145 mg. in three hours. The specimens of fasting urine of the children showed no sugar. After the ingestion of dextrose some of the subjects had varying amounts of sugar in the urine. Some of the children seemed to have a diminished renal threshold for sugar, since sugar (1 plus and 2 plus) was found in the urine when the blood sugar was at a level of from 115 to 167 mg.

ARTERIOVENOUS DIFFERENCE IN BLOOD SUGAR

It had been suggested that the lack of muscular activity or lack of muscular utilization of sugar was the cause for the abnormal results obtained in the sugar tolerance tests. If this were the case one would expect the physically inactive patients to have diminished differences in the simultaneous values for arterial and for venous blood sugar.

To study this aspect of the problem further the arteriovenous difference in the blood sugar was studied in 18 inactive adults and 16 inactive children and compared with the normal difference. For practical purposes the concentration of sugar in the blood obtained from the capillaries of the finger by puncture is practically identical with the concentration of sugar in the blood simultaneously obtained from the radial artery. This has been well demonstrated by Langner and Fies,[9] Hagedorn,[10] Foster,[11] Jonas[12] and Blistein,[13] even in the presence of considerable arteriovenous differences. In addition, Langner and Fies[9] found this to be true whether there is a free flow of blood from the finger or whether the finger is squeezed. Consequently, in this paper I refer to the sugar in the capillary blood as arterial blood sugar.

The results of the tests for arteriovenous differences appeared quite significant after the ingestion of dextrose. These results are illustrated in chart 4.

In the inactive adults the usual arteriovenous difference in the fasting blood sugar was approximately 8 or 10 mg. per hundred cubic centimeters. A few had equal values for arterial and the venous fasting blood sugar, and in others the venous content was 3 or 4 mg. higher than the arterial. At the peak of the blood sugar curves after the ingestion of dextrose the arteriovenous differences of the blood sugar generally ranged from 15 to 30 mg. per hundred cubic centimeters, and on rare occasions the difference was as much as 40 to 50 mg. In three hours the arteriovenous difference in the blood sugar was approximately 15 or 20 mg. In comparison, the active adults after the ingestion of dextrose had arteriovenous differences of the blood sugar of 10 to 20 mg. at the peak of the blood sugar curves and of approximately 10 mg. in three hours.

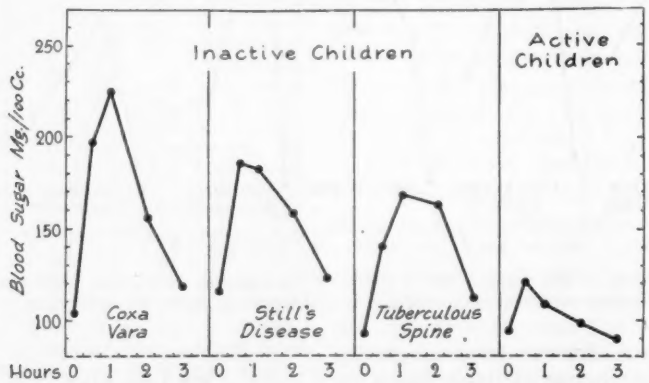

Chart 3.—Characteristic blood sugar curves following the ingestion of dextrose for 16 nondiabetic children with certain diseases who had been confined to bed from six months to thirteen years, compared with typical sugar tolerance in active children.

9. Langner, P. H., and Fies, H. L.: Blood Sugar Values of Blood Obtained Simultaneously from the Radial Artery, Antecubital Vein, and the Finger, Am. J. Clin. Path. **12**:559, 1942.

10. Hagedorn, H. C.: Om sukkerprocenten i vena mediana cubiti, Ugesk. f. læger **82**:796, 1920.

11. Foster, G. L.: Studies on Carbohydrate Metabolism: I. Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, J. Biol. Chem. **55**:291, 1923.

12. Jonas, L.: A Note on Cutaneous Venous Blood Sugar Difference in Normal Males and Females and in Thyroid Disease, J. Clin. Investigation **12**:139, 1933.

13. Blistein, I.: La glycemie arterielle et veineuse, Arch. internat. de méd. exper. **8**:25, 1933.

In the children the arteriovenous differences in blood sugar were similar to those found in the adults, as illustrated also in chart 4.

In many of the patients with diminished sugar tolerance the arteriovenous differences were even greater than those ordinarily found in normal persons. This strongly suggests that even though patients are physically inactive their muscles utilize sugar normally. Consequently, the result obtained in the inactive patients requires another explanation.

COMMENT

The results of this investigation show that persons with certain pathologic conditions who are confined to bed for considerable periods have diminished dextrose tolerance. The blood sugar curves are of the diabetic type. It might be assumed that because of the physical inactivity the muscles do not use up as much dextrose as they do when active. However, such a hypothesis can be questioned, because these patients do not eat as much as they do when active and consequently there is not as much available sugar to metabolize. Furthermore, the arteriovenous difference in the blood sugar curves after the ingestion of dextrose was found to be as great as or even greater than the normal difference. This suggests that the muscle of the inactive patient is capable of utilizing as much sugar as that of the normal person. It would appear that prolonged physical inactivity allows the pancreas to rest and results in sugar tolerance curves similar to those obtained when the pancreas is put at rest after insulin is administered in the treatment of nondiabetic malnutrition [4] or when animals are placed on a high fat diet.[14] Under these conditions the pancreatic islets are relieved of the necessity for secreting insulin, and the insulin content of the pancreas is reduced. Consequently, the reaction of the islets of the pancreas to stimulation by dextrose becomes less than normal. Furthermore, with physical inactivity there is not the demand for rapid storage and utilization of sugar that is present in active persons, and this results in less demand on the pancreas and ultimately in diminished function of the pancreas.

There have been reports of tests showing diminished sugar tolerance in patients with certain diseases who have been ill for some time. Although the cause for this is unknown, attempts were made to correlate the disease with the disturbed carbohydrate metabolism. Nissen and Spencer [15] found that sugar tolerance tests showed abnormal results in 57 per cent of 222 patients with arthritis and that age, sex, blood pressure and focus of infection had no apparent relation to these results.

Diminished dextrose tolerance has been observed in certain patients with tuberculosis by Langston [16] and by Kramer.[17] Rohdenburg, Bernhard and Krehbiel [18] studied a variety of

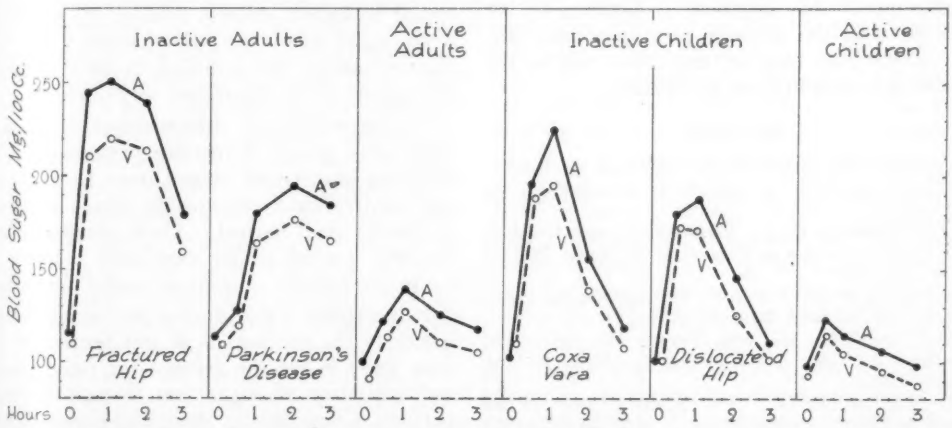

Chart 4.—Illustrations of capillary-venous differences in sugar tolerance curves for 18 adults and 16 children confined to bed for long periods, compared with corresponding values for active adults and children. *A*, capillary blood; *V*, venous blood.

14. Haist, R. E.; Campbell, J., and Best, C. H.: The Prevention of Diabetes, New England J. Med. **223**:607, 1940.

15. Nissen, H. A., and Spencer, K. A.: Sugar Tolerance in Arthritis, New England J. Med. **210**:13, 1934.

16. Langston, W.: Glucose Tolerance Test, J. Lab. & Clin. Med. **7**:293, 1922.

17. Kramer, D. W.: Glucose Tolerance Curves in Pulmonary Tuberculosis, J. Lab. & Clin. Med. **18**:1212, 1933.

18. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, O.: A Study of Sugar Mobilization Based upon Two Hundred and Twenty-Eight Human Cases, Am. J. M. Sc. **159**:577, 1920.

diseases, especially cancer,[19] and found that many diseases are accompanied by hyperglycemia after ingestion of dextrose and that the concentration of the blood sugar is not the sole factor in the development of glycosuria. A reduction in sugar tolerance may occur in old age, according to Deren,[20] Hale-White and Payne[21] and Marshall,[22] especially in the presence of disease. I believe that the diminished sugar tolerance noted in old persons is due not to age but rather to the inactivity associated with age and that if these people were normally active their sugar tolerance would likely be normal. In this connection the effect of inactivity would vary with individuals.

A disturbed carbohydrate metabolism may be found in patients with mental disease in an institution, as shown by Robinson and Shelton,[23] who noted that this was common in 69 consecutive patients with nervous or mental disease. It would appear that inactivity is common to the patients with the diesases mentioned and that this factor may play an important role in the diminished carbohydrate metabolism.

SUMMARY

A study was made of the effect of prolonged physical inactivity on the dextrose tolerance of 86 nondiabetic patients—70 adults and 16 children—who had been confined to bed for one month to thirteen years by various pathologic conditions. A comparison was made between the dextrose tolerance of these patients and that of active adults and children.

Is was found in general that the sugar tolerance was diminished in the patients who had been confined to bed for considerable periods. The fasting blood sugar in these cases ranged from 70 to 130 mg. per hundred cubic centimeters, and the fasting urine was free from sugar. After the ingestion of dextrose the concentration of blood sugar rose to abnormal levels, the maximum being 364 mg., and varying amounts of sugar were found in the urine at various times. In many of the adults there was a high renal threshold for dextrose. In some patients who later became ambulatory for several months the sugar tolerance returned to normal. Age did not appear to have a definite relation to the diminished sugar tolerance. Hypertension, vascular disease, obesity and infection in themselves did not appear to be significant as causes.

The arteriovenous differences in the blood sugar of a group of inactive persons after the ingestion of dextrose ranged from 15 to 50 mg. per hundred cubic centimeters, which is normal or greater than normal. These results indicate that the muscles of the physically inactive patients are capable of utilizing sugar normally.

It is suggested that during prolonged physical inactivity the pancreas is at rest because in this state there is not the demand for rapid storage and utilization of sugar that there is in active persons. Consequently, there may ensue diabetic-like reactions to dextrose tolerance tests even with normal fasting levels of blood sugar.

189 Bay State Road.

19. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, O.: Sugar Tolerance in Cancer, J. A. M. A. **72**:1528 (May 24) 1919.

20. Deren, M. D.: Dextrose Tolerance in the Aged, J. Lab. & Clin. Med. **22**:1138, 1937.

21. Hale-White, R., and Payne, W. W.: The Dextrose Tolerance Curve in Health, Quart. J. Med. **19**:393, 1926.

22. Marshall, F. W.: The Sugar Content of the Blood in Elderly People, Quart. J. Med. **24**:257, 1931.

23. Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients, J. A. M. A. **114**:2279 (June 8) 1940.

ACUTE SUPPURATIVE BRONCHOPNEUMONIA

HAROLD NEUHOF, M.D., AND ALEXANDER THOMAS, M.D.*
NEW YORK

The type of bronchopneumonia characterized by suppuration within the parenchyma has been known by various names. We shall employ the term "suppurative bronchopneumonia," [1] which has been used for many years at the Mount Sinai Hospital. As evidence that pathologists have been long acquainted with the disease, Kaufmann's statement [2] that "pyogenic organisms may lead to suppuration, purulent liquefaction or abscess formation in the lung" may be quoted. It can also be assumed that clinicians know and recognize the disease. Nevertheless, suppurative bronchopneumonia under any name has been the subject of only few and fragmentary contributions [3] by pathologists and clinicians alike. The subject, which has been under study by us for many years, is presented at this time because the current literature, which deals so fully with other forms of pneumonia, omits reference to it. The obvious possibilities in treatment with penicillin would appear to make imperative a more general recognition of the features of the disease.

The pertinent literature on the subject is so scanty that a brief survey will suffice. At the outset reference can be made to papers [4] which deal chiefly with the differentiation between aerobic and anaerobic (putrid) pulmonary suppuration. There usually is omitted evidence to suggest any relationship to a preexisting pneumonia, which may have been taken for granted. An indirect relationship to pulmonary suppuration is occasionally pointed out in instances of empyema in which bronchial fistulas are noted. Thus Hedblom [5] referred to such empyemas as "presumably derived from small superficial abscesses" of the lung.

A feature of the literature which should be singled out for special mention is the bacteriologic aspect of bronchopneumonia. Two types of pyogenic pulmonary suppuration, the influenzal and that due to Friedlaender's bacillus, have been thoroughly studied. Because of their distinctive characteristics, however, which are distinctly different from those which we shall describe, they will not receive further consideration in this paper. Staphylococcic suppurative pneumonia has been the subject of a number of contributions, particularly in recent years, the reports dealing for the most part with small groups of cases. The pediatric literature has been particularly concerned with staphylococcic pneumonia (Kanof, Kramer and Carnes,[6] Gaspar,[7] Clements and Weens [8] and others). Neuhof and Berck [9] have called attention to the frequency of staphylococcic empyema in infants and young children. The impression that suppurative pneumonia is rare is to be noted also in the literature on the streptococcic pneumonias. Thus, Lawrence and Sutliff,[10] in a review of cases of pneumonia in which hemolytic streptococci were found in the sputum, reported but 2 instances in which pulmonary suppuration due to that organism was found at postmortem ex-

* Now Captain, Medical Corps, Army of the United States.

From the Medical and Surgical Services and the Laboratories of the Mount Sinai Hospital.

1. The disease is not given a distinctive listing in the *Quarterly Cumulative Index Medicus*. There are two forms of suppurative pneumonia, due respectively to the Bacillus influenzae and Friedlaenders bacillus, which are listed but, as will be indicated, they will be omitted from consideration because of many different features which they possess.

2. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 400.

3. With the exception of the special variety of staphylococcic pneumonia, as will be noted.

4. (*a*) Eisendrath, D. N.: Surgery of Pulmonary Abscess, Gangrene and Bronchiectasis Following Pneumonia, Philadelphia M. J. **8**:786, 1901. (*b*) Sauerbruch, F.: Die Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1920, vol. 1, p. 540. (*c*) Meyer, W.: Observations on Lung Suppuration and Its Treatment, Arch. Surg. **6**:361 (Jan., pt. 2) 1923. (*d*) Kline, B. S., and Berger, S. S.: Pulmonary Abscess and Pulmonary Gangrene, Arch. Int. Med. **56**:753 (Oct.) 1935.

5. Hedblom, C. A.: Pulmonary Suppuration, M. Rec. **96**:441, 1919.

6. Kanof, A.; Kramer, B., and Carnes, M.: Staphylococcus Pneumonia, J. Pediat. **14**:712, 1939.

7. Gaspar, I. A.: A Study of Primary Staphylococcic Pneumonias, New York State J. Med. **41**:834, 1941.

8. Clemens, H. H., and Weens, H. S.: Staphylococcic Pneumonia in Infants, J. Pediat. **20**:281, 1942.

9. Neuhof, H., and Berck, M.: Staphylococcic Empyema and Pyopneumothorax: Pathogenesis, Pathology, Symptoms and Treatment, Arch. Surg. **30**:543 (March) 1935.

10. Lawrence, E. A., and Sutliff, W. D.: Streptococcus Pneumonia, New York State J. Med. **40**:1233, 1940.

amination. In a series of 911 cases of pneumonia described by Cecil and Lawrence [11] only 3 per cent were reported to be due to hemolytic streptococci and no mention was made of any special characteristics of the streptococcic group. The rarity of pulmonary suppuration as a complication of bronchopneumonia was referred to by Senerchia and Livengood [12] in their report of 8 cases of pneumonia in which Streptococcus viridans was cultured from the sputum. There are scattered references to the occurrence of suppurative pneumonia ascribed to pneumococci.

The pathologic features of suppurative bronchopneumonia are scarcely mentioned in textbooks that devote considerable space to other bronchopneumonias. However, two unusual types have been described: aputrid necrosis, first reported by Kessel,[13] and a form of extreme necrosis of the lung (necrotizing pneumonia) reported by French authors.[14] In the former, pulmonary cavitation was discovered on routine roentgen examination—and such cavities were found to heal spontaneously within a short time—or was found as an incidental lesion at autopsy. The microscopic study of autopsy material led to the belief that the lesion was of vascular origin, in the form of thrombosis in the pneumonic area followed by infarction and secondary necrosis. The necrotic pneumonia of French authors has been reported as a rare lesion characterized by widespread destruction of pulmonary tissue. Moolten [15] described a fatal case and laid stress on the factor of necrosis.

From the foregoing paragraphs it can be said that while suppurative pneumonia under various names has long been known to exist the disease has not been the subject of more than a fragmentary presentation. Our survey of the pathogenesis, pathology, roentgen features, clinical manifestations and therapy is based on an analysis of 120 well documented cases which have been studied at the Mount Sinai Hospital over a period of more than ten years. These cases do not comprise all the instances of suppurative pneumonia observed in that period. Many cases of mild and of transient disease have been omitted because they were not adequately proved or documented and because we wished to concentrate attention chiefly on the more distinctive cases.

Special attention will be devoted to the clinical forms of the disease because its many variations comprise its most interesting as well as its most distinctive feature. Roentgenograms will be employed to illustrate clinical forms as well as the evolution of the disease.

The 120 cases which comprise our series were all cases of suppurative pneumonia due to aerobic pyogenic organisms. The anaerobic infections of the lung (putrid pulmonary abscess) have no place in this paper. They comprise a separate and unrelated entity, and their inclusion, except for considerations of differential diagnosis, would serve no useful purpose. There will also be excluded all forms of suppurative pneumonia or pulmonary suppuration which can be regarded as secondary, such as suppuration secondary to bronchial neoplasm, tuberculosis or bronchiectasis. The pulmonary suppurative foci which occur in septicemia are of a different as well as a specific nature and will therefore not be considered. The reason for excluding pneumonias due to the Friedlaender or influenza organisms has already been stated.

Clinical and roentgen features as well as data obtained at operation or at autopsy comprise the basis for study of the 120 cases. Cultures of pus obtained under favorable conditions confirmed the diagnosis in many instances. It can be stated at once that a variety of aerobic organisms were cultured. We shall show that little if any difference could be ascertained in the pathologic conditions or in the clinical course in relation to the causative organism.

INCIDENCE

In contradistinction to the statements in the literature on the subject, our evidence is that suppurative bronchopneumonia is not rare. We have stated that the 120 cases of our series were gathered during a period of approximately ten years and that not a few cases of mild disease and incompletely documented cases were omitted. We now realize also that in the earlier years, before the features of suppurative pneumonia were appreciated by us, a considerable number of cases were overlooked. Thus suppurative bronchopneumonia should not be regarded as a rare disease.

There appears to be a seasonal incidence of suppurative bronchopnuemonia which corresponds generally to other varieties of pneumonia. In our series the number of cases reached a peak in the beginning of December and extended

11. Cecil, R. L., and Lawrence, E. A.: Pneumonia in Private Practice, J. A. M. A. **111**:1889 (Nov. 19) 1938.

12. Senerchia, F. F., Jr., and Livengood, H. R.: Streptococcus Viridans Pneumonia, New York State J. Med. **41**:143, 1941.

13. Kessel, L.: The Clinical Aspect of Aputrid Pulmonary Necrosis, Arch. Int. Med. **45**:401 (March) 1930.

14. Letulle, M., and Bezançon, F.: La pneumonie dissequante necrotique, Ann. de med. **12**:1, 1922.

15. Moolten, S. E.: Pulmonary Infection and Necrosis in Diabetes Mellitus, Arch. Int. Med. **66**:561 (Sept.) 1940.

through March. It then tapered off to a low point in July, but cases were encountered throughout the year. In scarcely any of the cases was there a history suggesting epidemic features. Emphasis should be placed on the fact that the disease occurs as a rule in previously healthy persons. Thus many of the severe and fatal cases were encountered amongst such patients.

Cases of the disease appear to be about equally divided between the sexes. It is seen in all age groups, with a disproportionate preponderance in children. One third of the patients were children under the age of 10 years (see the table). The disproportion may be accounted for by the high incidence of the staphylococcic variety of suppurative pneumonia in infants[9] and the frequency of the pneumococcic variety in young children. We assume that the disease is not uncommon as a terminal infection in old and debilitated or cachectic persons, but we can draw no conclusions from our limited experience with such cases.

Age Distribution

Age, Years	Cases
Under 1	10
1- 9	30
10-19	10
20-29	18
30-39	15
40-49	15
50-59	9
60-69	11
70 and over	2

PATHOGENESIS

The evidence in our series of cases justifies only an assumption that the pathogenesis of suppurative bronchopneumonia is similar to that of other bronchopneumonias. In a large percentage of the cases there was a history of an infection of the upper respiratory tract which immediately preceded the onset of the pulmonary disease. It will be pointed out shortly that the suppurative pneumonias involve bronchopulmonary segments as in bronchopneumonia. Thus a similar pathway of descending infection appears likely in suppurative bronchopneumonia. We stated that the disease usually is encountered in previously healthy persons. In a few cases the disease occurred in persons with diabetes, but there appeared to be no disproportionate increase in incidence, and the extent of the lesion

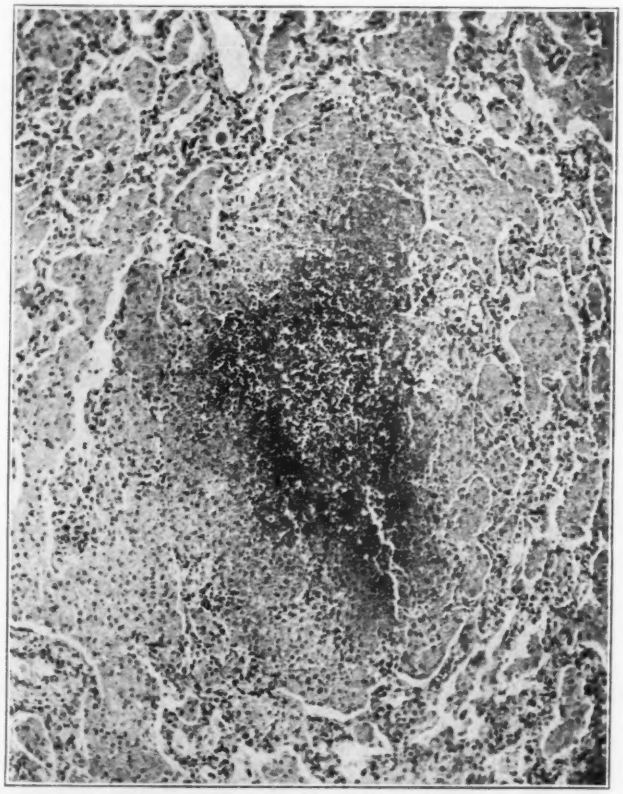

Fig. 1.—Necrosis in an area of suppurative bronchopneumonia.

was not appreciably greater than that seen among normal persons.

GENERAL AND CLINICAL PATHOLOGY

As in many other conditions, autopsy is likely to reveal chiefly the most advanced stages of the disease, and therefore reliance on autopsy alone may lead to false impressions. In our series of cases considerable knowledge of the gross pathologic changes was obtained at operation (for pulmonary abscess and for the pleural complications of suppurative pneumonia) and will be discussed under appropriate captions.

purative process itself (fig. 1). In several instances, there were, in addition, vascular lesions in the nature of acute nonspecific arteritis and thrombosis (fig. 2). These were apparently the result of intense infection and led to further necrosis and suppuration secondary to anemic infarction.

There were identified roentgenologically, at operation and at autopsy, instances in which the degree of destruction of pulmonary tissue was outstanding. In some of these cases there were large cavities with limited surrounding inflammatory and suppurative zones. In others the

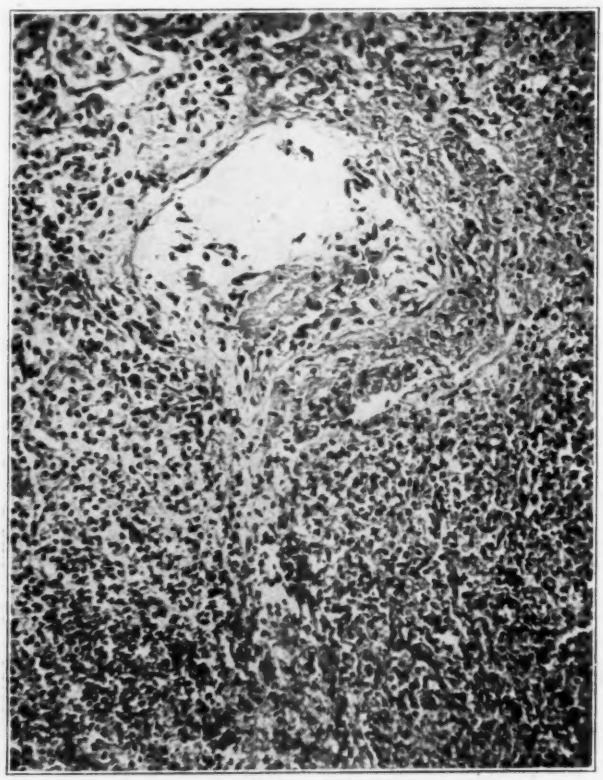

Fig. 2.—Suppurative bronchopneumonia with acute nonspecific arteritis and thrombosis.

The pathologic conditions as noted at autopsy will be briefly considered. The lesions were often multiple. Each consisted of a severe bronchopneumonia with varying degrees of suppuration and necrosis. Single or multiple abscesses were usually present. It should be noted that the lesion or lesions were of substantial proportions, each involving much or all of one or more bronchopulmonary segments.[16] Microscopic examination revealed that necrosis, which was almost invariably present, was due to the suppurative process itself. In several instances, there were, in addition, vascular lesions in the nature of acute nonspecific arteritis and thrombosis. These were apparently the result of intense infection and led to further necrosis and suppuration secondary to anemic infarction.

There were identified roentgenologically, at operation and at autopsy, instances in which the degree of destruction of pulmonary tissue was outstanding. In some of these cases there were large cavities with limited surrounding inflammatory and suppurative zones. In others the cavities contained small amounts of pus or necrotic tissue. To this distinctive and not rare type in which the element of necrosis is spectacular one of us (H. N.) has applied the term "necrosuppurative bronchopneumonia."

In view of the fact that suppurative bronchopneumonia is a lesion which occupies a bronchopulmonary segment,[16] overlying pleuritis is of necessity a constant feature. In most of the cases the pleuritis is severe. Because the suppurative pulmonary lesion often extends to the surface of the segment or perforates into the pleural space, suppurative pleuritis is of frequent

16. Glass, A.: Bronchopulmonary Segments, Am. J. Roentgenol. **31**:328, 1934.

occurrence and is often found at autopsy. The pleural complications will be discussed in a consideration of the surgical aspects of the disease.

Suppurative bronchopneumonia can be defined as an infection in which either complete recovery or death usually occurs in the acute stage. Only infrequently does the lesion within the lung go on to a chronic phase with the formation of a chronic abscess or chronic interstitial pneumonia and bronchiectasis. Some of the characteristics of persistent or spreading suppurative bronchopneumonia which are of surgical interest because of complications will be subsequently discussed. Pulmonary abscess and suppurative pleuritis will be taken up in a consideration of the surgical aspects of the disease.

It should be pointed out here that the pathologic features of suppurative bronchopneumonia set the disease apart from putrid pulmonary infections. However, the two diseases appear to be confused at times according to the literature, and emphasis therefore should be placed on the differences which exist. Putrid pulmonary infections are almost always localized to one part of the lung, and thus are in striking contrast to suppurative pneumonia, which is often diffuse and situated in a number of segments. For example, suppurative pneumonia which has gone on to a nonputrid pulmonary abscess may be encountered in one part of the lung at the same time as areas of suppurative pneumonia in other parts. In other instances nonputrid pulmonary abscesses are present in several segments of one lung or in both lungs. Another distinguishing feature of the pathology is the extent of the pneumonitis which surrounds an existing pulmonary abscess. In the case of a putrid lesion the surrounding pneumonitis usually occupies a well defined and limited zone, whereas in suppurative pneumonia a collection of pus when present is often situated in the midst of an extensive pneumonic lesion. Only in those exceptional instances in which suppurative pneumonia goes on to typical abscess formation does the pathology resemble that of putrid pulmonary abscess. It is therefore incorrect to say that all cases of abscess of the lung belong in the same category and require the same treatment, regardless of whether the sputum has a foul or a nonfoul odor and whether the infection is anaerobic or aerobic.

BACTERIOLOGY

The bacteriologic examinations in our series of cases were made from cultures of pus when pus was obtainable. The most reliable source of pus was operation, under which circumstances there was obviously the best chance for the disclosure of the causative organism. Occasionally pus was obtained directly from the pulmonary lesion. Our remarks concerning the bacteriology of suppurative bronchopneumonia are based on cultures obtained from empyemas or from pulmonary abscesses and not from sputum. Anaerobic as well as aerobic cultures were taken. In the great preponderance of cases a single pyogenic organism was obtained in pure culture. In no instance was an anaerobic organism cultured. The organisms most frequently encountered in pure culture were Staphylococcus aureus, hemolytic streptococci and pneumococci (of various types). Of special interest is the isolation of Streptococcus viridans in pure culture in a number of cases. In view of the fact that this organism could not be regarded as a contaminant, its presence in pure culture warrants the assumption that it is the causative organism in not a small proportion of cases of suppurative bronchopneumonia. It can be added here that the clinical course of Str. viridans infections was not appreciably different from that of suppurative bronchopneumonia due to other aerobic organisms.

The reasons for our unwillingness to place reliance on cultures of sputum as a satisfactory means of determining the bacteriology of the pulmonary infection should be stated. In some instances the same organism as that which existed in the pulmonary or pleural lesion was found in the sputum. Occasionally the same organism was obtained in pure culture. In the preponderance of cases, however, cultures of sputum revealed not only mixed organisms but organisms different from those obtained from the pus in the lung or pleura. Furthermore, cultures of sputum taken at different times disclosed different organisms in some cases. Because of these observations we believe that positive statements concerning the bacterial causation of suppurative bronchopneumonia should not be made on the basis of cultures of the sputum.

ROENTGENOGRAPHIC FEATURES

There appear to be no reports in the literature concerning the roentgen features of suppurative bronchopneumonia other than those from the Mount Sinai Hospital group. Bizarre and surprising patterns in cases of pneumonia undoubtedly have been seen and variously interpreted by many, yet their relationship to suppurative bronchopneumonia has not been noted. A number of years ago one of us (H. N.) came to realize that certain patterns were characteristic of the disease. Distinctive and sequential films from many cases were collected. As a result of their study a single feature, the presence of one or more areas of rarefaction in the midst of pneumonic infiltration, was found to be roentgenologically pathognomonic. We have called

attention to this feature at various times. In 1938 we indicated its significance in relationship to suppurative bronchopneumonia and to aerobic pulmonary abscess.[17] Sussman[18] in 1940 referred to it in a consideration of the roentgen aspects of nonputrid pulmonary suppuration. The proportion of cases of suppurative bronchopneumonia in which characteristic areas of rarefaction will be revealed in roentgenograms cannot be stated. They are common in our series, which consists however of specially selected cases. As will be emphasized, they may also be revealed in laminagrams when not visible on ordinary roentgenograms.

In the absence of rarefaction there is no one pathognomonic roentgenologic sign of suppurative bronchopneumonia. However, there are a number of distinguishing features which are encountered so frequently that they can be regarded as characteristic of the disease. Rabin[19] has called attention to these features in his division of the roentgen manifestations of suppurative bronchopneumonia into six varieties: (1) interstitial infiltrations about the bronchi, blood vessels and interlobular septums; (2) homogeneous densities, either single or multiple, of lobular, segmental or lobar distribution; (3) changes indicating the presence of focal, segmental or lobar atelectasis or emphysema; (4) multiple areas of rarefaction indicating the presence of a destructive process within the lung or bronchi; (5) single abscess cavities of varying size, and (6) collections of fluid and air within the pleural cavity which may obscure the intrapulmonary changes. It should be noted that these features may exist separately or in various combinations. Indeed, the possibilities of combinations either in the same pulmonary field or in different fields are almost endless. As has already been pointed out, spontaneous resolution and healing may occur in lesions in which, according to roentgenograms, there appears to be extensive destruction of pulmonary parenchyma.

Concerning atelectasis in pneumonia, with or without emphysema, bronchial obstruction is generally assumed to be the sole cause. As evidence in support of this view it can be said that atelectasis occurs more often in infants and young children, apparently because of an inability to expel tenacious bronchial exudate by coughing. Without entering into a discussion of this debatable subject, it can be pointed out that other causes for atelectasis have been postulated. In any event one may say that atelectasis as such should be regarded as only an incidental feature of the pathologic changes of suppurative bronchopneumonia.

Of special interest are the cases in which roentgenograms reveal large, so-called balloon cavities. Such thin-walled cavities may be found to persist in films after apparently complete subsidence of pulmonary infection. A mechanical factor which seems to be chiefly responsible for these balloon cavities has been described by Moolten.[20] Whether the mechanism is a ball valve action in a bronchus, centrifugal traction on the lung[20] or is differently conceived,[21] the important points to note are that the lesion is not in the nature of extensive pulmonary destruction, that spontaneous disappearance is likely to occur and that there are no indications for surgical (or other) treatment. The roentgen and clinical differentiation of balloon cavities from pulmonary abscess complicating suppurative bronchopneumonia offers no difficulties.

Sectional roentgenography (laminagraphy) has been referred to in a foregoing paragraph as of value in revealing the existence of areas of rarefaction in the midst of apparently solid pneumonic infiltration. There were a few cases in this series in which the diagnosis of suppurative bronchopneumonia remained in doubt after the usual films were studied. In every instance laminagrams revealed the existence of areas of rarefaction. We do not know that laminagraphy would invariably disclose areas of rarefaction in cases of suppurative bronchopneumonia but have gained the impression that cavitation would be seen in at least the preponderance of cases of the severe type. Laminagraphy should therefore be employed when a definite diagnosis is required and the usual roentgenograms do not reveal areas of rarefaction in the midst of pneumonic infiltration.

SYMPTOMS AND PHYSICAL SIGNS

Suppurative bronchopneumonia can be defined symptomatically as an acute infection which is often preceded by an infection of the upper respiratory tract and which is characterized by fever, cough and the expectoration of purulent sputum. Thoracic pain occurs early in the course

17. Neuhof, H., and Touroff, A. S. W.: Acute Aerobic (Nonputrid) Abscess of the Lungs, Surgery **4**:728, 1938.

18. Sussman, M.: The Roentgen Aspects of Non-Putrid Pulmonary Suppuration, Am. J. Roentgenol. **44**:345, 1940.

19. Rabin, C. B.: Roentgen Features of Suppurative Bronchopneumonia, J. Mt. Sinai Hosp. **8**:32, 1941.

20. Moolten, S. E.: Mechanical Production of Cavities in Isolated Lungs, Arch. Path. **19**:825 (June) 1935.

21. Caffey, J.: Regional Obstructive Pulmonary Emphysema in Infants and in Children, Am. J. Dis. Child. **60**:586 (Sept.) 1940.

of suppurative pneumonia and is sufficiently common to be regarded as a feature of the disease. It is of pleuritic character, usually sharp and localized, and occasionally so severe as to comprise the outstanding symptom. The variations of these typical clinical features are numerous and will be discussed later in some detail. Indeed, they must be known in order to recognize suppurative bronchopneumonia in all its protean forms.

Fever is usually moderate, at times on a high level, but may be irregular or even remittent. Emphasis should be placed on the fact that it may be mild and out of proportion to the extent and the intensity of the pneumonic lesion as revealed in roentgenograms. Indeed, there are instances in which the febrile course has largely subsided at a time when roentgenologic evidence of an extensive lesion still exists.

Except in infancy or early childhood expectoration of purulent sputum or of frank nonfetid pus occurs in almost all cases and should be regarded as the distinctive clinical feature of the disease. The amount of purulent sputum usually is substantial, a common daily range being from 1 to 6 ounces (30 to 180 cc.) or even more. When scanty it consists of small quantities of thick, tenacious purulent sputum. Occasionally expectoration of pus may be scanty or absent at the outset, to become profuse later in the course of the disease. Signs of toxemia are seen within the first week in severe infections, and prostration often is extreme under such circumstances. When the disease is protracted, toxemia and expectoration are usually extreme. We wish to repeat, however, that the clinical course cannot be measured by the extent of the pulmonary lesions as revealed in roentgenograms.

Before discussing physical signs it should be noted that dyspnea is not a uniform feature of suppurative bronchopneumonia, even in its most acute form. Omitting a discussion of the factors which are generally responsible for it, it should be pointed out that in suppurative bronchopneumonia dyspnea is most commonly observed when pleural penetration or infection either is impending or has already taken place. There are no distinctive physical signs of suppurative bronchopneumonia. The signs are similar to those of other bronchopneumonic lesions. They often are scanty in comparison to the extent of the lesion as revealed by roentgenogram or at operation. Physical signs of cavitation should not be expected even when cavities are of substantial dimensions. On the other hand, suppurative pleuritis generally produces characteristic physical signs, particularly on percussion. Breath sounds become distant or absent in any gross form of pleural invasion (generalized effusion, pneumothorax or pyopneumothorax).

Examination of the blood often reveals a moderate to severe leukocytosis, although a white cell count below 10,000 is not rare. Anemia is present in protracted infections, which are usually accompanied by pronounced toxemia.

DIFFERENTIAL DIAGNOSIS

Suppurative bronchopneumonia usually can be diagnosed readily on the basis of the clinical features alone. A knowledge of the many clinical varieties of the disease is necessary for its recognition. The roentgenographic features are characteristic in a substantial proportion of the cases. In doubtful instances laminagraphy may reveal areas of rarefaction and thereby clarify the diagnosis. However, a protracted clinical course may raise the question of the existence of some other disease. Thus, a course extending over several weeks may suggest pulmonary tuberculosis or neoplasm. Concerning the latter, bronchoscopy may prove to present positive evidence and should, therefore, not be omitted in doubtful cases. As to tuberculosis, it has been our experience that if the sputum is frankly purulent the absence of tubercle bacilli on several examinations precludes its existence. When the sputum is scanty, the examination of spreads of pus obtained by bronchoscopy may be required in order to establish the presence or absence of tuberculosis. In cases of shut-off putrid pulmonary abscess (which are exceptional) the sputum may be quite free from foul odor. The diagnosis may not be established until (1) fetid sputum appears, (2) foul pus or odor is revealed by bronchoscopy or (3) a putrid empyema establishes the diagnosis. The problem of roentgen differentiation of suppurative bronchopneumonia from forms of virus pneumonia has arisen. At first sight, mottled patches of bronchopneumonia with suggestive areas of rarefaction indicated the diagnosis of suppurative bronchopneumonia. However, the absence of purulent sputum combined with severe prostration, the leukopenia and the subsequent resolution (according to roentgenograms) of the lesion without the development of cavitation excluded the diagnosis of suppurative pneumonia. It is our belief that the simulation of cavitation on the roentgenogram is due to the pattern made by mottled patches of bronchopneumonia. Finally, mention should be made of unusual suppurative pulmonary lesions, such as actinomycosis, which may at times simulate suppurative bronchopneumonia so closely that the correct diagnosis can be established only after prolonged observation and study.

CLINICAL VARIETIES

The general description of the clinical manifestations of suppurative bronchopneumonia has been given. We wish to present here the clinical varieties which have been encountered. Since unusual manifestations which are of frequent occurrence really characterize the disease, the descriptions of the clinical varieties will be followed in each instance by one or more illustrative cases. A number of unusual or extreme examples have been purposely chosen. The 120 cases which comprise this series fall into four main groups but the classification is largely one of convenience and some measure of overlapping will be noted. The complications are included in the classification because they comprise an important aspect of the disease.

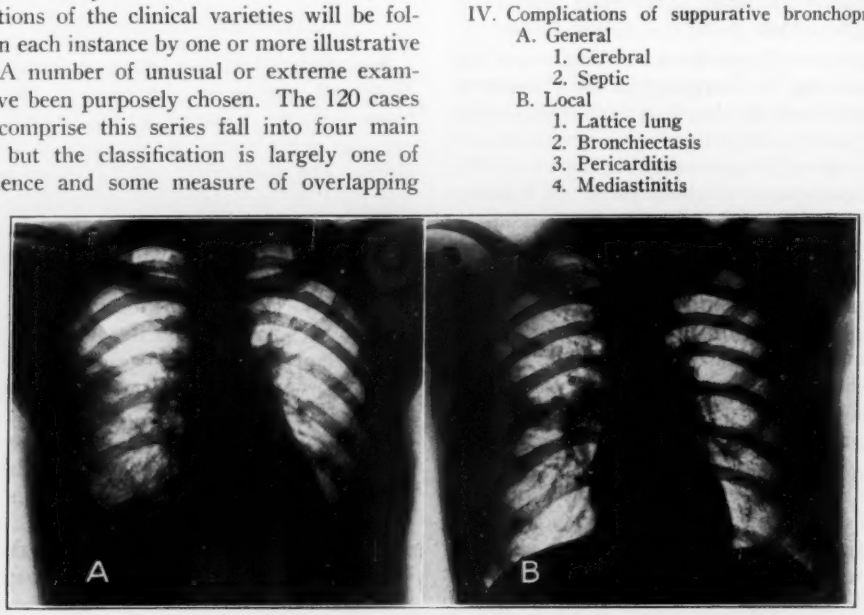

Fig. 3 (case 1).—*A*, infiltration in the middle portion of the right pulmonary field, with cavitation and fluid level; *B*, eight days later, spontaneous resolution.

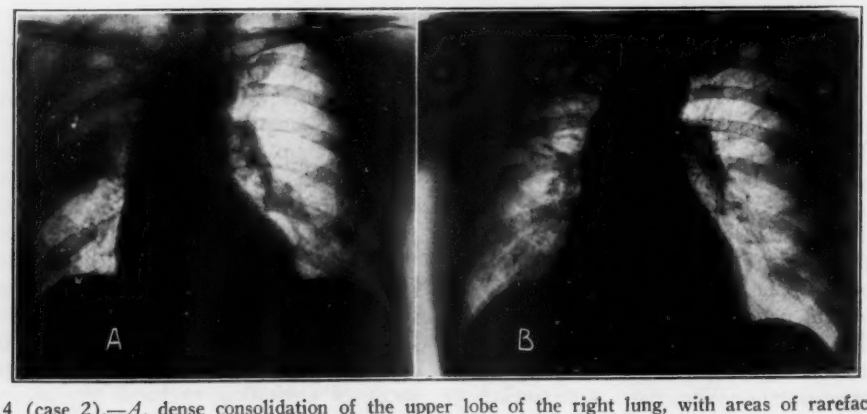

Fig. 4 (case 2).—*A*, dense consolidation of the upper lobe of the right lung, with areas of rarefaction and fluid levels; *B*, eight weeks later, in process of resolution.

CLASSIFICATION

I. Basic forms
  A. Localized suppurative bronchopneumonia
  B. Diffuse suppurative bronchopneumonia
II. Secondary suppurative bronchopneumonia
  A. Postoperative
  B. In cachexia
  C. From other predisposing causes
III. Surgical forms
  A. Pulmonary abscess
  B. Empyema and pyopneumothorax
    1. With proved pulmonary focus
    2. Without proved pulmonary focus
IV. Complications of suppurative bronchopneumonia
  A. General
    1. Cerebral
    2. Septic
  B. Local
    1. Lattice lung
    2. Bronchiectasis
    3. Pericarditis
    4. Mediastinitis

I A. Localized Suppurative Bronchopneumonia.—This is the most common form in which the disease is manifested. The lesion occupies a more or less substantial portion of one or two adjacent bronchopulmonary segments, and the clinical course usually lacks surgical or other complicating features. In the following 3 illus-

trative cases the first was chosen as typical of the most benign form, and the second was selected because it was characterized by a severe and toxic course. The third is presented because there was a unique opportunity to observe the pathologic conditions of suppurative bronchopneumonia in a patient who recovered.

CASE 1.—C. A., a 25 year old woman, had a three week history of cough, pain in the right side of the chest, low fever and expectoration of thick greenish sputum. Roentgen examination showed infiltration in the axillary segment of the upper lobe of the right lung with a circular area of increased aeration; the second roentgenogram revealed a definite cavity with a small fluid level. The course was benign; there was low grade fever for three days, and the temperature was normal thereafter. Roentgenography showed progressive clearing. On follow-up examination the patient was entirely well, and the roentgenogram was normal.

CASE 2.—J. F., a 49 year old man, had a 4 week history of fever and cough which was productive of purulent sputum. A roentgenogram showed dense consolidation within the upper lobe of the right lung. There was a severe septic course for ten weeks, with local extension of pneumonitis and on the roentgenogram appearance of areas of rarefaction with fluid levels. He raised profuse purulent sputum throughout the course. Convalescence was gradual, with complete recovery and a negative roentgenogram. A bronchogram after recovery was negative.

CASE 3.—G. L., a 52 year old man with mild diabetes, was admitted to the hospital with a two week history of dyspnea, fever and cough, with scanty expectoration. Roentgen examination showed dense infiltration in the middle third of the right lung, with small irregular areas of increased aeration. Physical signs suggested empyema, and aspiration revealed pus. On the diagnosis of encapsulated empyema, thoracotomy was done. There were well defined pleural adhesions sealing off the free pleural space. The underlying lung was infiltrated, and wherever traversed by the aspirating needle small collections of pus were encountered. There was no single large collection of pus to be drained, and the exploration of the lung was discontinued. The clinical course apparently was uninfluenced by operation. Emphasis should be placed on the fact that despite the pathologic alterations noted at operation healing occurred, with complete disappearance of all roentgen evidence of pulmonary infiltration.

I B. Diffuse Suppurative Bronchopneumonia.—This type is characterized clinically by a more severe or prolonged course. Fatal cases are encountered in this group. Clinically, the outstanding feature is profuse purulent expectoration in virtually all instances. Roentgenologically, the lesion differs from the preceding by a more widespread invasion with ill defined limits. There may be involvement of portions of the adjacent or the more remote lung which occurs often enough to be regarded as distinctive. Three illustrative cases will be presented: A case of its occurrence in a child, a case of its occurrence in an adult, and a fatal case.

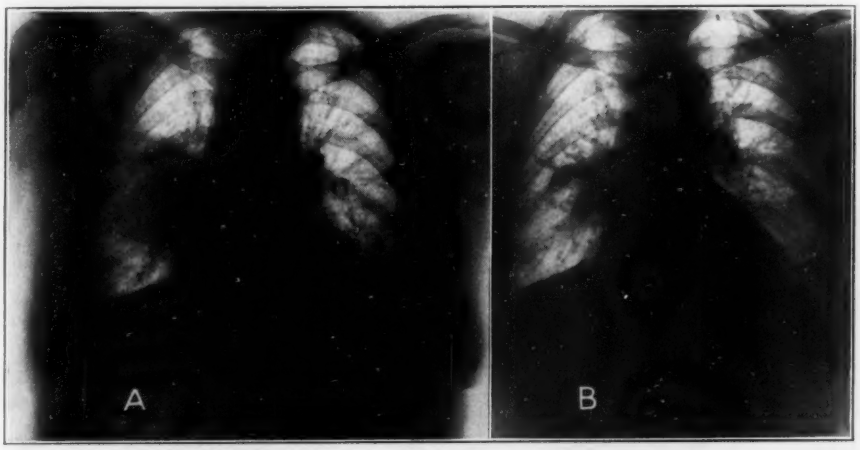

Fig. 5 (case 3).—*A*, preoperative roentgenogram, showing dense infiltration of right lung with small irregular, faint areas of increased aeration; *B*, two weeks later, in process of resolution.

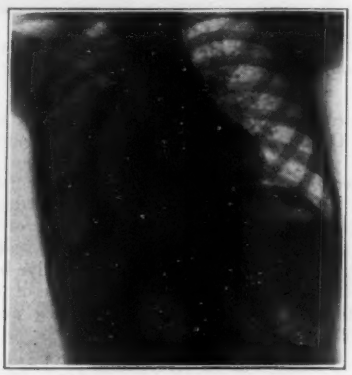

Fig. 6 (case 4).—Diffuse pneumonic infiltration of most of the right lung, with numerous areas of rarefaction and exudate in the right pleura.

CASE 4.—L. A., a 4 year old boy, presented a history of cough and fever for eight days. Diffuse pneumonic

infiltration of most of the right lung with numerous small areas of rarefaction was found on roentgen examination. The clinical course was extraordinarily mild, with slight fever for several weeks and expectoration of moderate quantities of purulent sputum. Successive roentgenograms in the hospital revealed increase in the areas of rarefaction, some with fluid levels, and an exudate in the right pleura. Progressive absorption and finally disappearance of all areas of pneumonic infiltration and rarefaction occurred. The final roentgenogram was normal. Follow-up for several years showed that the boy was entirely well.

CASE 5.—S. L., a 37 year old man, presented a four week history of moderate fever, cough and expectoration of small amounts of purulent sputum. A roentgenogram revealed infiltration in the midportions of both lungs, with a number of cavities, some with fluid levels. Numerous examinations of sputum did not show acid-fast bacilli. There was gradual improvement with normal temperature after three weeks. The final roentgenogram was normal.

CASE 6.—N. T., a 45 year old man, entered the hospital with a six day history of fever, pain in the left side of the chest, cough, and expectoration of purulent sputum. On admission, there were signs of pneumonia over the upper lobe of the left lung. There was a progressive downhill course with spread of the pneumonia to the lower lobe of the left lung and the entire middle lobe of the right lung, development of cardiac irregularities and pericardial friction rub ending in death. Autopsy revealed confluent suppurative bronchopneumonia of the lower and upper lobes of the left and of the middle lobe of the right lung and acute serofibrinous pericarditis.

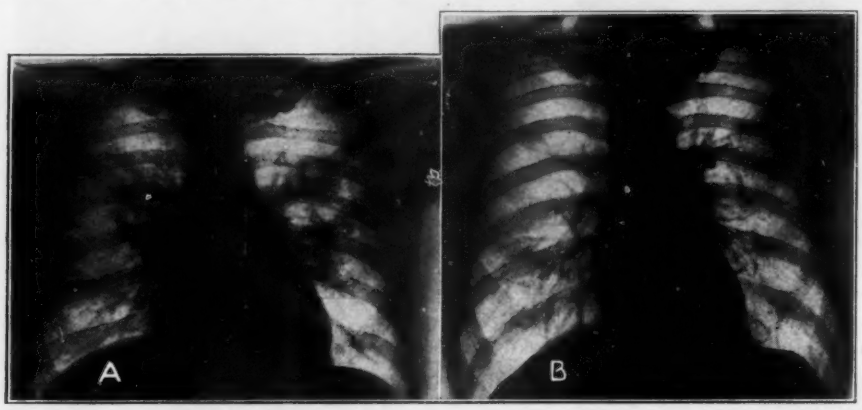

Fig. 7 (case 5).—*A*, bilateral infiltration, with a number of cavities resembling tuberculosis; *B*, four weeks later, resolution.

II A. Postoperative (Secondary) Suppurative Bronchopneumonia.—Since we are concerned with suppurative bronchopneumonia without obvious cause ("primary suppurative bronchopneumonia," for want of a better designation) cases of suppurative bronchopneumonia which occur postoperatively or in cachexia or which are of other more or less obvious cause do not belong here, strictly speaking. However, postoperative suppurative bronchopneumonia, in particular, warrants some consideration because the pathologic features so closely resemble or are perhaps identical with those of the type under consideration. Cases are frequently encountered and are well known in surgical services. In our series of 120 cases only 5 cases of severe postoperative suppurative bronchopneumonia are included, making a disproportionately small number in relation to the whole. One illustrative case will be cited.

CASE 7.—On B. D., a 65 year old man, a subtotal gastrectomy for carcinoma of the stomach had been performed. Onset of fever occurred twelve hours postoperatively. Moderate fever continued thereafter, with purulent sputum, dyspnea and cyanosis. Death occurred on the ninth postoperative day. At autopsy diffuse necrotizing suppurative bronchopneumonia, with several areas of subpleural abscess formation, and diffuse purulent bronchiolitis were found.

III A. Pulmonary Abscess.—As has already been indicated, this lesion should be regarded as an infrequent complication of suppurative or necrosuppurative bronchopneumonia. It has been fully described elsewhere.[17] The frequent occurrence of more or less localized collections of pus in suppurative bronchopneumonia may be mentioned. However, it is only when a stage is reached in which collections of pus are no longer merely incidental to the surrounding suppurative bronchopneumonia that a pulmonary abscess can be said to exist. In typical cases the abscess is solitary, of substantial proportions, situated superficially within the lung and overlain by agglutinating visceroparietal pleural adhesions. It contains a varying amount of pus and presents the orifices of one or more bronchi. A case will be presented which is of particular interest because the complete evolution of the disease is visible in the roentgenograms.

CASE 8.—B. R., a 54 year old man, was admitted to the hospital with an eight day history of fever and slight

cough. A roentgenogram showed pneumonic segmental infiltration in the upper lobe of the left lung. An irregular febrile course followed. After several days expectoration of purulent sputum began, and it later became more profuse. There was no response to chemotherapy. Successive roentgenograms showed development of a fluid level in the lesion and progressive localization with abscess formation. After five weeks in the hospital the abscess was drained through sealing off adhesions in one stage. On culture of pus from the abscess Streptococcus intermedius was isolated. The postoperative course was characterized by prompt subsidence of the fever, cough and expectoration, and progressive healing of the cavity and wound. Follow-up examination showed the patient to be entirely well. Roentgenographic examination revealed slight residual fibrosis, and a bronchogram was normal.

pleural lesion. In the case of anaerobic (putrid) infections of the lung, the tendency to localization of the pleural infection is pronounced. The causative lesion in the lung is a more or less obvious perforated pulmonary abscess. Hence pyopneumothorax is the rule. In cases of suppurative bronchopneumonia the tendency to localization often is slight, especially in children. Thus, in not a few of the cases of its occurrence in children the disease is characterized by a diffuse subtotal or even total empyema. The extent of the air component is unpredictable. Thus, there are instances in which the pyopneumo-

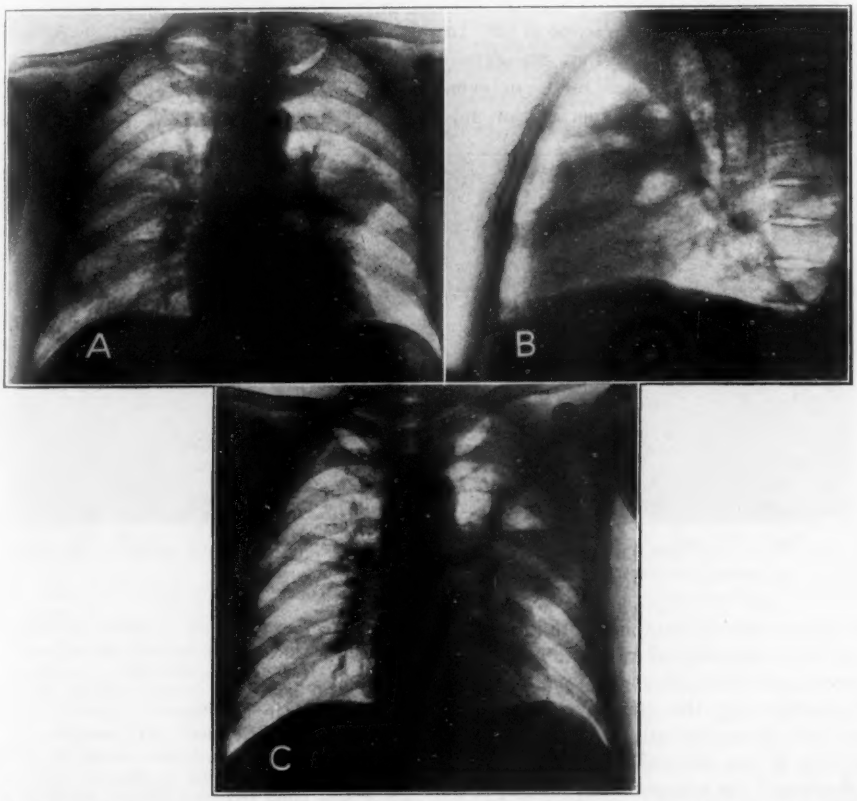

Fig. 8 (case 8).—*A*, pneumonic infiltration in the middle of the left pulmonary field; *B*, (lateral projection) beginning cavitation on the same date; *C*, one month later, just before operation, showing localization of the lesion with development of a pulmonary abscess.

III B. Empyema and Pyopneumothorax.—As a complication of suppurative bronchopneumonia of any variety pleural invasion may exist in the form of a localized or diffuse collection of pus, and the empyema may or may not contain air. Indeed, there are cases of bilateral empyema in our series in which one side contained air and the other side did not, and cases of multiple empyema over one lung with the same differences. Many factors lead to the varying characteristics of the thorax is obvious and extreme even in young children or infants, whereas in other cases little or no air is present.

The chief purpose of the foregoing discussion is to stress an important fact which warrants general recognition. In some cases in which the empyema at first contains no air according to roentgenograms reexamination later discloses the presence of a pyopneumothorax. In other cases operation for airless empyema may disclose an

obviously ruptured abscess of the lung. The reason for the absence of air under such circumstances is of interest. We believe that the perforated focus is compressed by the accumulation of fluid in the pleura and is thus incapable of supplying enough air from its communicating bronchus to be visualized in a film. Thus we have seen instances in which at open operation for encapsulated, non-air-containing empyema there was the orifice of a perforated pulmonary abscess with a blowing bronchial fistula immediately following the evacuation of pus. It was evident that the latter permitted the bronchial communication to open up and that the compression of the empyema previously prevented the escape of air. In other cases it may be postulated that the pulmonary abscess cavity becomes collapsed (or even healed) by the mechanism of a perforation followed by the pressure of intrapleural fluid and air. Indeed, we have encountered more than one large pyopneumothorax in which at the time of operation or subsequently the causative pulmonary focus was not demonstrated. Lastly, it can be assumed that at the time of a minor operation (closed drainage) the evacuation of an empyema may release the pressure on a collapsed perforated abscess and thereby open up a bronchial communication which did not exist theretofore. Thus, we have seen instances in which closed drainage of an empyema was accompanied by under water escape of several ounces of pus without air, to be followed by the bubbling of large quantities of air. The proof that an empyema was derived from a perforated pulmonary focus was lacking in only a small proportion of our cases. In these instances there may be postulated a small, so-called cortical pulmonary abscess or seepage from the underlying inflamed lung, as in lobar pneumonia.

Two illustrative cases will be presented, 1 of empyema with a proved perforated pulmonary focus and the other a case of pyopneumothorax without such a proved focus.

CASE 9.—A. M., a 53 year old man, entered the hospital with a three day history of severe bronchopneumonia of the lower lobe of the right and of the left lung. There was a stormy course for several weeks, with development of roentgen evidence of a right pleural effusion, followed by evidence of an encapsulated right paravertebral empyema. Thoracotomy was performed and a localized empyema with a ruptured large pulmonary abscess and a bronchial fistula in the floor of the empyema cavity when pus was removed were found. The opening of the pulmonary abscess was enlarged and the empyema drained in one stage. Culture of pus yielded a pneumococcus of type IV. Recovery was rapid and complete.

CASE 10.—J. G., a 4 year old boy, had a ten day history of infection of the upper respiratory tract and fever. Signs of pneumonia of the middle and lower lobes of the right lung were observed on admission. After three weeks in the hospital physical signs of a large pyopneumothorax became evident and were confirmed by roentgen examination. An emergency stab thoracotomy and under water drainage of pus and air, followed several days later by open thoracotomy and drainage, was performed. At operation no bronchial fistula or pulmonary abscess could be demonstrated. Culture of pus revealed a pneumococcus of type I. There was rapid recovery, and on follow-up the roentgenogram was normal.

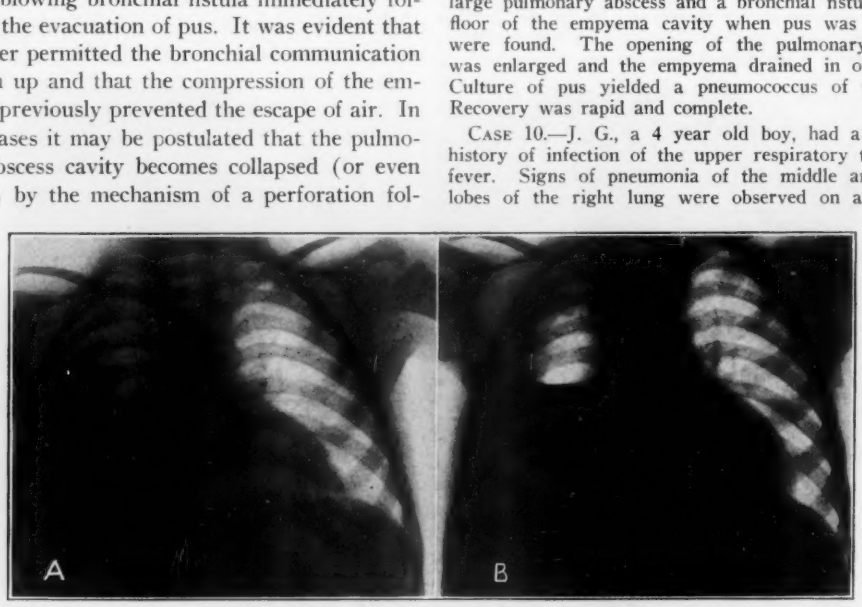

Fig. 9 (case 10).—*A*, diffuse pneumonic infiltration of the right lung after two weeks of hospitalization; *B*, six days later, pyopneumothorax.

IV A. General Complications of Suppurative Bronchopneumonia.—Of the general complications, which are varied, we have selected two groups because of their gravity.

1. Cerebral: Evidence of cerebral infection existed in a number of the cases of severe or fatal disease. There were symptoms and signs of a cerebral abscess in 4. In all, the disease was fatal, and all terminated with suppurative meningitis. The focal signs of involvement of the brain were not typical, and precise localization of the lesion was not possible. In contrast to cerebral

abscesses of other origin, it may be said of this group that the cerebral lesion was invariably unfavorable for surgical drainage. Only in 1 instance did the pulmonary lesion appear to be undergoing retrogression at the time of the onset of symptoms referable to the complicating cerebral abscess. The report of this case follows:

CASE 11.—S. A., a 36 year old man, had been subjected to thyroidectomy for diffuse toxic goiter three weeks earlier at another hospital. Operation was followed by cough and fever, and there were increase in fever and onset of pain in the lower left part of the chest on the day before his admission to this hospital. Roentgen examination showed pneumonic infiltration of the lower lobe of the left lung, with abscess formation and empyema. Operation consisted of thoracotomy and drainage of two perforated pulmonary abscesses with encapsulated empyema. Culture of pus revealed Str. viridans. Postoperatively the pulmonary status improved gradually. The onset of tetany was controlled by specific therapy. Signs of cerebral abscess were observed one week postoperatively, and lumbar puncture provided evidence of purulent meningitis.

2. Septic: It has already been pointed out that metastatic abscesses of the lung occur as part of the picture of septicemia. In a sense these pulmonary foci may be regarded as foci of suppurative pneumonia. However, as has been indicated, the clinical and focal features are different from those of the latter disease, and embolic pulmonary abscesses, which have not been included in this paper, should not be confused with multiple areas of suppurative bronchopneumonia.

Septic foci derived from suppurative bronchopneumonia are rarely seen, although the suppurative focus in the lung can be logically regarded as a potential source of septic invasion of the blood stream. The direct source can be visualized as a suppurative phlebitis or arteritis in the midst of an area of suppurative bronchopneumonia (fig. 2). Thus, multiple abscesses either in the pulmonary circuit or in the systemic system may be derived from such vascular sources. In the following case an unusual picture appears to conform with this concept.

CASE 12.—C. C., a 2 year old girl had a two week history of infection of the upper respiratory tract and fever. She was admitted to the hospital acutely ill with high fever. The roentgenogram showed a large pulmonary abscess with a fluid level in the lower lobe of the right lung. Culture of blood yielded 60 colonies of Staph. aureus per cubic centimeter of blood. Operation, performed on the day after admission, consisted of a one stage pneumonotomy and drainage of a large abscess of the lower lobe of the right lung; the appearance of early lattice lung was noted. Later drainage of many superficial abscesses due to Staph. aureus was performed. The residual pulmonary activity was closed with a fat graft. Follow-up showed complete recovery.

IV B. Local Complications of Suppurative Bronchopneumonia.—Local complications are those which occur within or adjacent to the lung during the time of the disease or after it has run its acute course.

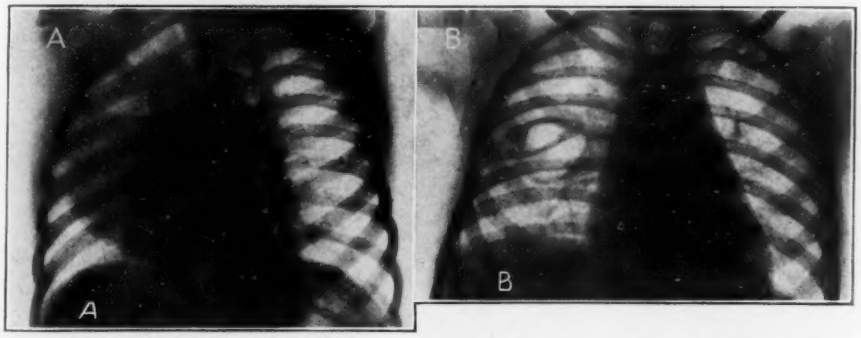

Fig. 10 (case 12).—*A*, large pulmonary abscess of the lower lobe of the right lung on admission; *B*, follow-up roentgenogram after closure of the residual cavity with a fat graft (the patient completely well).

1. Lattice lung: Lattice lung, generally regarded as a sequel of bronchopneumonia, has been found by us to be present during the acute phase. This fact not only is of importance clinically but is of interest to students of the disease because it establishes clearly the occasionally destructive nature of the lesion which warrants the term "necrosuppurative bronchopneumonia." We have seen two or more bronchopulmonary segments occupied by lattice lung with its many bronchial openings as early as two or three weeks after the onset of the pulmonary infection. Attention should be directed to the disproportion which may exist at times between a large area of lattice lung and the actual extent of destruction of pulmonary tissue. Mechanical forces, especially eccentric traction, may play so great a role that a given area of lattice lung appears to represent a much larger area of loss of pulmonary tissue than subsequently proves to be true. Two cases will be presented in order to depict the acute

and the chronic phase of lattice lung and their management.

CASE 13.—I. H., an 11 month old boy, was admitted to the hospital with a history of five days of fever, cough and signs of pneumonia of the upper part of the right lung. A roentgenogram after one week revealed a shadow in the right upper part of the chest with three fluid levels. Thoracotomy was performed, and a large multiloculated perforated pulmonary abscess with extensive destruction of the upper lobe of the right lung and lattice lung were found. On culture of pus a pneumococcus of undetermined type was isolated. Postoperatively there was progressive improvement, and the large residual pulmonary cavity was closed with a fat graft. During the follow-up period of five years the wound healed, the boy became free of symptoms and roentgenograms have been normal.

CASE 14.—R. B., a 5 year old boy was admitted to the hospital with a history of pneumonia followed by empyema one and one-half years before admission, treated by repeated aspirations of pus. Roentgen examination showed a right pyopneumothorax. At operation the right lung was found collapsed, and there was a large excavation in the lower lobe with numerous blowing bronchial fistulas. Culture of pus yielded a pneumococcus of type X. Several operations were performed in the next three years, chiefly thoracoplasties. Finally lobectomy, partly successful, was followed by fat graft for the closure of the remaining portion of lattice lung. Since then the patient has been well, with a healed wound but severe scoliosis. Recently the wound reopened, with the appearance of a small bronchial fistula.

2. Bronchiectasis: The subject of bronchiectasis as a complication or sequel of suppurative bronchopneumonia is a large one but will be only briefly considered. There has been little opportunity to observe the actual development of bronchiectasis in association with suppurative bronchopneumonia. In some instances we have noted by bronchography a transient bronchiectasis as a complication of the acute phase. The bronchographic demonstration of restitution to normal without any residue of bronchial dilatation is of particular interest. It is safe to say that bronchiectasis as a complication is much more common in infants and young children than in adults. Of the illustrative cases of its occurrence in young patients, 1 was chosen for its demonstration of the reversibility of bronchiectasis and the other because of the evolution of bronchiectasis in a mild form.

CASE 15.—L. S., a 16 year old boy, had a three week history of fever and expectoration of thick odorless sputum. Pneumonic infiltration of the lower lobes of both lungs and a suggestion of a fluid level in the lower lobe of the right lung were observed on roentgen examination. Bronchoscopic examination showed pus in the bronchi of both lower lobes. There was a gradual improvement, the fever and expectoration subsiding after one week in the hospital. A bronchogram after subsidence of the fever revealed dilatation of the bronchi of the lower lobe of the right lung, with abrupt ending of some third degree bronchi in globular dilatations. On follow-up the patient was entirely well. A bronchogram after two months showed persistence of bronchial dilatations; one year later, the bronchogram was normal.

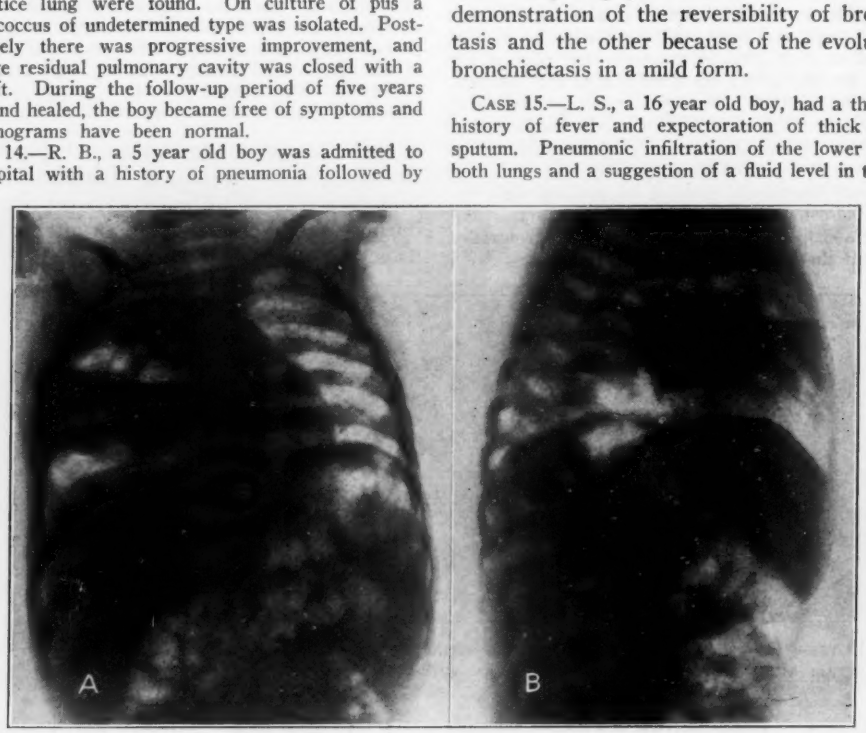

Fig. 11 (case 13).—*A*, extensive lesion of the upper lobe of the right lung, with three large fluid levels; *B*, lateral view, showing great extent of the lesion.

CASE 16.—C. E., a 14 year old girl, had a three week history of fever, pain in the left side of the chest and mucoid expectoration. The roentgenogram on admission showed pneumonia of the posterolateral portion of the lower lobe of the left lung and another, ten days later, showed atelectatic pneumonia of the same segment. The fever subsided after a few days, and expectoration became profuse and purulent. A bronchogram after four weeks showed bronchiectasis of the lower lobe of the left lung, with shrinkage of the lobe. Pneumothorax therapy was followed by cessation

of cough and expectoration. Pneumothorax was discontinued after one year. The patient has been well since then, with normal roentgenograms after several years.

3. Pericarditis: Suppurative pericarditis is the third local complication for consideration and occurs as a result of direct extension from the adjacent area of suppurative bronchopneumonia. Theoretically, therefore, this variety of suppurative pericarditis should be regarded as amenable to surgical relief, in contrast to suppurative pericarditis of metastatic origin. However, the infection within the pericardium is so insidious and in some respects so incidental to severe suppurative bronchopneumonia that the diagnosis is not often made, and when it is made, the lesion is rarely amenable to surgical relief. It is found not infrequently at autopsy. In our series there was 1 clinical case of suppurative pericarditis

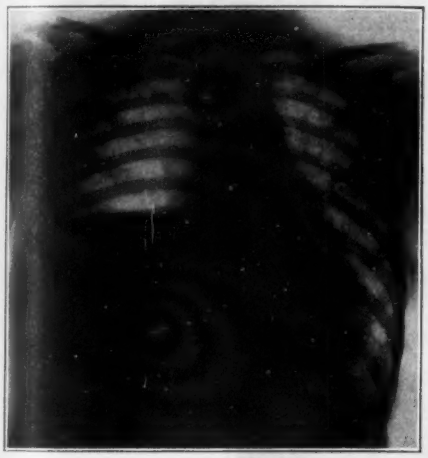

Fig. 12 (case 14).—Chronic right pyopneumothorax with collapsed lung.

complicating bilateral suppurative bronchopneumonia and empyema. Cure followed drainage of the pericardium.

4. Mediastinitis: Suppurative mediastinitis occurs occasionally as the result of direct extension from areas of suppuration within the lung and pleura. In our series it was noted as an invasion of the posterior mediastinum in fatal cases and was apparently incidental and without clinical manifestations. Suppurative mediastinal lymphadenitis was also noted occasionally at autopsy in cases of widespread suppurative bronchopneumonia.

TREATMENT

Brief consideration of the treatment of suppurative bronchopneumonia will suffice at this time because the disease is to be regarded as self limited, essentially unaffected by treatment and going on to recovery, death or surgical complications. There has been ample opportunity to employ chemotherapy, including the newer sulfonamide drugs, in our series of cases, and the results have been disappointing. Indeed, a response to treatment which could be regarded as definite or decisive was seen so rarely that we are in considerable doubt as to the advisability of employing chemotherapy. At most its use for only a few days appears warranted, to be discontinued if the clinical and roentgen picture of continuing suppuration in the lung is noted.

Concerning serum therapy for the pneumococcic variety of suppurative bronchopneumonia, definite results were not noted. Thus, the statement made concerning the use of the sulfonamide drugs appears to apply with at least equal force to serum therapy.

In contrast to the foregoing methods, supportive medical treatment has undoubtedly been of value in aiding in the recovery of a substantial proportion of the patients with severe suppurative bronchopneumonia. Rest in bed, maintenance of nutrition, administration of oxygen and liberal transfusions of blood have been factors which appeared not only to aid in increasing resistance but actually to facilitate recovery. Persistence in vigorous supportive therapy is indicated, particularly when the course is protracted, because recoveries which may not be anticipated will at times result.

PRINCIPLES OF SURGICAL MANAGEMENT OF PULMONARY AND OF PLEURAL COMPLICATIONS

Although characterized by suppuration, the disease does not often require surgical intervention so far as suppuration within the lung is concerned. Single or multiple suppurative foci of even large size may undergo spontaneous recession by drainage via the bronchi. By way of contrast, surgical intervention is frequently indicated for anaerobic infections of the lung (putrid pulmonary abscess) according to the views which we have maintained.[22] In various parts of this paper the pathologic and the clinical and roentgenologic manifestations of surgical complications of suppurative bronchopneumonia have been described. We wish to discuss here the principles of operative treatment of the complications in the lung and pleura.

Pulmonary abscess can be termed an unusual complication. Suppuration within the parenchy-

22. Neuhof, H., and Touroff, A. S. W.: Acute Putrid Abscess of the Lung: Principles of Operative Treatment, Surg., Gynec. & Obst. **63**:353, 1936.

ma is, of course, part of the disease, and coalescence of several adjacent purulent foci is undoubtedly of common occurrence. In a paper dealing with aerobic pulmonary abscess,[17] we classified the pulmonary suppurative lesions of the type of pneumonia under discussion into three groups: (1) pulmonary abscess in the midst of, and apparently an incidental part of, an extensive necrosuppurative bronchopneumonia; (2) pulmonary abscess as the prominent or predominating lesion but surrounded by a considerable area of necrosuppurative bronchopneumonia; (3) typical pulmonary abscess with a more or less sharply limited and narrow surrounding zone of infected lung. Our purpose in calling attention to this classification is to emphasize that surgical intervention is indicated only for the typical pulmonary abscess. Operative treatment employed for the other varieties not only is of no value but may lead to spread of the infection. Suppuration in the midst of pneumonic infiltration may eventually lead to typical abscess formation, but this evolution must be awaited for days or even weeks before one proceeds with operation. The evolution of such an abscess and its management is illustrated by case 8 and its accompanying roentgenograms. Roentgenograms are seen to provide the only guide to indicate the existence of a pulmonary abscess because the transition of symptoms from suppurative bronchopneumonia to abscess is too slight for clinical identification. In a study of the films special search should be made for additional pneumonic areas in the same or in the opposite lung, because the knowledge of the existence of such areas may lead to withholding operation even in cases of typical pulmonary abscess. In any event, a knowledge of their existence is essential in the decision as to

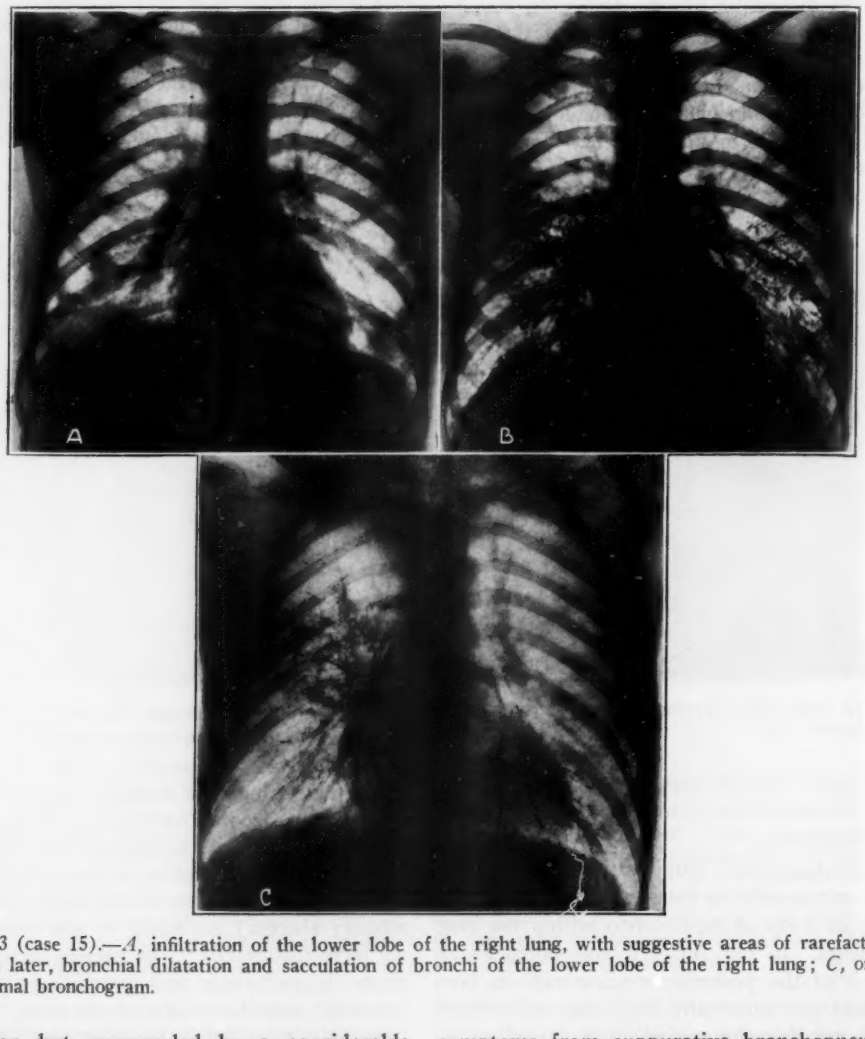

Fig. 13 (case 15).—*A*, infiltration of the lower lobe of the right lung, with suggestive areas of rarefaction; *B*, nine days later, bronchial dilatation and sacculation of bronchi of the lower lobe of the right lung; *C*, one year later, normal bronchogram.

operation and in interpretation in the event of an unsatisfactory postoperative course.

The operative treatment of the pulmonary abscess must be based on precise roentgen localization of the abscess. If there is any doubt as to the site of contact of the abscess with the thoracic parietes the spot localization method of Rabin [23] should be employed. In the appropriate section of this paper a pulmonary abscess was described as solitary, of substantial proportions, superficially situated within a pulmonary lobe and sealed off from the free pleura by visceroparietal agglutinating adhesions. Emphasis should be placed here on the necessity for traversing these adhesions in the one stage operation which we advocate. On the one hand, infection of the free pleura is a grave complication; on the other hand, the interference with coughing and expectoration which goes with a two stage operation will almost certainly lead to serious spread of the infection within the lung. But the most important objection to a one stage operation is the danger of infection of the pleura; hence the necessity for careful localization of the abscess followed by an exact one stage operation. The principle of the operation should consist of the entry into the abscess through its most superficial portion, where the shell of lung is thin, compressed and avascular, and the excision of the thin shell within the limits of pleural adhesions. Expectoration of quantities of pus, which characterizes the preoperative course, should subside promptly after a satisfactory operation. Reference should be made to the rare situation of an abscess facing a fissure, the diaphragm or the mediastinum. In such circumstances the abscess, although always situated superficially in the pulmonary lobe, may excite only local adhesions. Thus agglutinating visceroparietal adhesions may be absent, and a special surgical problem exists. We have discussed this problem elsewhere [24] as well as the technic of operation for pulmonary abscesses in usual situations.

Whereas pulmonary abscess comprises a complication of suppurative bronchopneumonia which permits of deliberate study, pleural complications require at times prompt surgical intervention. Thus it can be mentioned that (chiefly in infants and young children) an abrupt pleural invasion by rupture of a pulmonary abscess into the free pleural space produces a situation in which immediate surgical intervention (closed drainage) may be imperative in order to save life. The organism most often encountered in such cases in infants and young children is Staph. aureus. Indeed, these staphylococcic pneumonias are generally regarded as highly fatal, yet not a few patients can be saved by prompt recognition of the pleural complication and equally prompt surgical intervention.

The possible sources of a suppurative pleuritis are to be noted in the diagram which has been devised to indicate the surgical aspects of suppurative bronchopneumonia (fig. 14). The caption "Persistent or Spreading Suppurative Bronchopneumonia" is employed to indicate that the surgical (particularly the pleural) complications are derived usually from a persistence of or spread from the original focus. As can be seen from the diagram, suppurative pleuritis may be evolved directly by extension from the pulmonary focus or may be secondary to a segmental perforated acute abscess at the site of suppurative bronchopneumonia. It may also be secondary to smaller solitary suppurative foci or to one of a series of multiple pulmonary abscesses. In rare instances it is a complication of a subacute or a chronic pulmonary abscess. In any event, the evolution of the pleural lesion may be gradual, resulting in a well localized empyema. This slow evolution is characterized by relatively mild manifestations, by physical signs suggesting

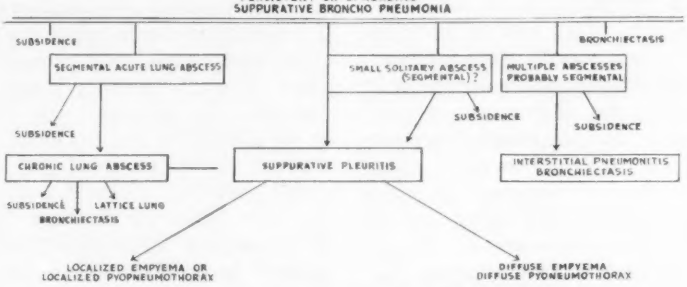

Fig. 14.—Surgical aspects of suppurative bronchopneumonia.

23. Rabin, C. B.: Precise Localization of Pulmonary Abscess; The "Spot" Method, J. Thoracic Surg. **10**: 662, 1941.

24. Footnotes 17 and 22.

pleural fluid and roentgenologically by the evidence of a localized pleural effusion. If the purulent effusion invades a region remote from the thoracic parietes, such as the paravertebral, interlobar or infrapulmonary areas, the evolution of the empyema may be obscured by adjacent "sympathetic" effusions of serous character situated in the parietes. It should be emphasized, however, that such effusions may reveal pyogenic organisms on culture. The localized collection of pus in the pleura may contain air or may be full of fluid. In the former case the evidence of communication with the bronchus is, of course, clear. The question of air-containing and non-air-containing empyemas was taken up in the section (III B) dealing with empyema and pyopneumothorax. From the viewpoint of surgical therapy the important fact is that a perforated pulmonary abscess often is the underlying cause, whether or not the empyema contains air.

The operative treatment of encapsulated empyema is thoracotomy and drainage. In the case of an empyema complicating suppurative bronchopneumonia emphasis should be placed on the frequency with which two or more encapsulations exist. Thus, identification and interrelation must be determined before operation by a study of roentgenograms taken in various positions. The encapsulations are usually intercommunicating, at times via a narrow neck. Occasionally, however, they are separate, in which circumstances they are derived from separate foci of suppurative bronchopneumonia. In several cases in our series they were bilateral. The basic principle of the operative treatment of encapsulated empyema is adequate drainage of every collection of pus. This often implies drainage to the site of the perforated pulmonary focus. At times the orifice of the latter must be enlarged for better drainage of the pulmonary abscess into the empyema space.

Concerning the principles of surgical treatment of diffuse empyema or pyopneumothorax, reference has already been made to imperative closed drainage for effusions under tension, most frequently occurring in infants and young children. There are two important facts to be emphasized: first, that such effusions with or without air are common and can be fatal in a short time if not definitively released, and, second, that they may occur abruptly and unexpectedly at an early stage (in time) of the pulmonary infection. Of course recovery will not occur merely because of timely and adequate treatment of such pleural effusions. In some of our cases the suppurative disease in the lung proved to be too extensive (as ascertained by autopsy) for a significant result to be anticipated. However, appropriate surgical treatment should be instituted regardless of the known or the assumed severity of the pulmonary lesion, for unexpected recoveries followlowing drainage have occurred in our cases.

In view of a conflicting literature we wish to place emphasis on our view that closed drainage is the only treatment for a rapid accumulation of pus and air or of pus alone in the free pleural space in cases of suppurative bronchopneumonia. It is the safest if not the sole means of influencing definitely not only the displacement of the heart and mediastinum but the infection in the pleural space. The clinical picture with which one may be faced can be restated. The patient, usually an infant or child, acutely ill with the manifestations of bronchopneumonia, becomes more acutely ill, often with dramatic and ominous suddenness. Cyanosis and dyspnea if already present become much more pronounced. The pulse races and becomes smaller. The heart is shifted toward the opposite side; there are the physical signs of fluid or of air and fluid, and in any event respiratory sounds are absent on the affected side. If a roentgenogram is taken it will reveal a shift of the heart, usually more pronounced than anticipated. Thus, there rarely is any doubt as to the diagnosis. To temporize with Potain aspiration on the assumption that the infection in the lung is too acute or the patient is too ill for the extremely simple operation of closed drainage may remove the only chance for recovery. We believe that the arguments which have been advanced elsewhere [25] in favor of closed drainage as against repeated aspiration apply with particular force to the situation under discussion.

Closed drainage may prove to be the sole procedure required for the treatment of the pleural complication. In most instances, however, open drainage, often carried to the site of a perforated pulmonary focus, will be required after the acute manifestations have subsided and the general condition is satisfactory. Occasionally pulmonary cavitation with its bronchial fistulas will persist after thoracotomy if the destructive lesion was extensive. This creates a special problem which we have usually solved by the simple expedient of free grafting of fat.[26] The latter procedure has also been employed in the acute stage in those rare instances in which dangerously large quantities of air escaping in the closed drainage system jeopardize the life of the patient.

25. Neuhof, H., and Hirschfeld, S.: Suppurative Pleuritis in Children: Its Pathogenesis, Diagnosis and Treatment, Am. J. Dis. Child. **44**:973 (Nov.) 1932.

26. Neuhof, H.: Free Transplantation of Fat for Bronchopulmonary Cavity, Ann. Surg. **113**:153, 1941.

PROGNOSIS

In the discussion of incidence we pointed out that the group of 120 cases on which this report is based was exceptional in the sense that it comprises only adequately proved and well documented cases and in large part of severe disease. Thus, the mortality of 24.2 per cent (29 deaths) in this series is unquestionably much too high for the disease as a whole, as is to be noted in the following brief statement concerning the causes of death in the 29 cases: Four occurred among cachectic persons or after major operations; in 5 instances death took place within a few days of the patient's admission to the hospital; in 4 fatal cases there was evidence of metastatic cerebral abscess. In most of the surgical cases, death was referable to the persistence or the spread of the disease within the lung.

In the section dealing with surgical aspects of suppurative bronchopneumonia we dealt with the subject of aerobic pulmonary abscess in which the differentiation was made from more or less localized suppuration in the midst of suppurative bronchopneumonia. Operation has been performed erroneously on the latter lesion with unsatisfactory or even fatal sequelae. On the other hand, emphasis should be placed on the excellent results of drainage operations for true pulmonary abscess. With precise roentgen localization a one stage operation performed through substantial pleural adhesions has resulted in cure in all the cases (15) in this series.

SUMMARY AND CONCLUSIONS

Suppurative bronchopneumonia, a descriptive term for an acute infection of the lung which has been long known under various names, is not rare and yet it is the subject of only a fragmentary literature. A systematic presentation of the subject has been attempted on the basis of a study of 120 well documented cases. The effort to include only proved cases resulted in a collection which contains a disproportionately high percentage of cases of severe forms of the disease.

The seasonal incidence of suppurative bronchopneumonia corresponds apparently with that of other forms of bronchopneumonia. As a rule the disease occurs in otherwise healthy persons. It apparently has a higher incidence in children than in adults.

Since the disease presents the features of an infection of the upper respiratory tract descending into bronchopulmonary segments, the pathogenesis of suppurative bronchopneumonia appears to be identical with that of nonsuppurative aspiration bronchopneumonia.

The pathologic features consist of a severe bronchopneumonia involving one, several or many portions of the lung or lungs. Substantial portions of bronchopulmonary segments are involved. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of lung, usually with the formation of single or multiple foci of liquefaction within areas of bronchopneumonia. Necrosis is at times outstanding and spectacular. The term "necrosuppurative bronchopneumonia" appears appropriate under such circumstances. The microscopic feature of suppurative bronchopneumonia is a combination of suppuration and necrosis in varying degree. In addition there is seen at times a nonspecific arteritis with thrombosis.

Suppurative pleuritis is a common complication. It may be circumscribed or diffuse, an empyema or a pyopneumothorax.

A true pulmonary abscess, a substantial collection of pus surrounded by a limited zone of pneumonitis, is an infrequent complication as compared with suppuration in the midst of a pneumonic area. A true abscess is situated superficially within a pulmonary lobe with overlying agglutinating visceroparietal adhesions. Adhesions are local and may not be visceroparietal when an abscess occupies one of the specified rare sites.

There is no distinctive bacteriologic agent for suppurative bronchopneumonia. One or more of the aerobic pyogenic organisms, most commonly Staph. aureus, hemolytic streptococci and pneumococci, are encountered. A pure culture of a single organism is the rule. Str. viridans is encountered as the sole organism in a substantial proportion of the cases. There appear to be no distinctive features of suppurative bronchopneumonia which can be related to the infecting organism, although it should be noted that the staphylococcic variety occurs characteristically in infants and young children. The only reliable cultures are those of material obtained by aspiration through the thorax or at operation. Cultures of sputum have proved to be unreliable in determining the causative organism.

The roentgen features are extremely varied and often bizarre. The six main types which are set forth may exist singly or in various combinations. One or more areas of rarefaction in the midst of pneumonic infiltration comprise the characteristic feature. This roentgen evidence of

suppurative bronchopneumonia, which can be regarded as pathognomonic, is not seen in all cases. It may be revealed by laminagrams when not visible in ordinary films.

The essential symptoms are initial thoracic pain which is at times severe, cough, expectoration of substantial quantities of purulent sputum (in adults) and fever. The physical signs are not distinctive.

The clinical forms of suppurative bronchopneumonia are varied, and a knowledge of the variations is required in order to recognize the disease in one of the protean forms in which it is manifested. The forms are somewhat arbitrarily classified under four headings: basic, secondary, surgical and general and local complications.

When suppurative bronchopneumonia pursues a prolonged course differentiation must be made from other causes of pulmonary suppuration, notably tuberculosis, neoplasm, fungous infection and even putrid pulmonary abscess.

Suppurative bronchopneumonia, including the necrosuppurative variety, is a self-limited disease which is not materially influenced by any of the currently employed sulfonamide compounds or by serum therapy (in the group of cases due to pneumococci). The treatment is primarily supportive and when vigorously pursued may greatly facilitate recovery.

Surgical complications within the thorax are common, comprise an important aspect of the disease and will be recognized promptly if the suppurative nature of the disease is kept in mind. Pulmonary abscess is an unusual complication. A one stage operation was followed by recovery in all cases.

The mortality in the reported series of 120 cases was high because of the inclusion of a disproportionately high percentage of cases of severe forms of the disease. The mortality of suppurative bronchopneumonia is due in large part to intrathoracic complications.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1944

NEUROSIS AND THE WAR

STANLEY COBB, M.D.
BOSTON

The time has not yet come when one can thoroughly discuss the psychiatric problems of World War II, but the subject is so important that a preliminary review is worth while. The data are accumulating all too rapidly and many papers have been written, but most of the more important observations are in publications still "restricted" by the military authorities. The American papers available deal largely with induction centers, training camps and morale. Interesting as these may be, they do not attack the crux of the situation, the acute nervous breakdown of the soldier in combat. The English literature has more papers about the acute psychiatric disorders of battle. The survivors from Dunkirk provided a rich material [1] and since then the aviators [2]; but even these papers do not provide answers to the fundamental questions, which will be available only when more facts are accumulated and a more mature tolerance smoothes out the polemic tendency of some writers to support one or another of the "schools" of psychiatric thought.

A paper by Grinker and Spiegel [3] has been released in Solomons and Yakovlev's "Manual of Military Neuropsychiatry," which gives one the most up-to-date picture of psychiatric treatment in the zone of combat. There is also a short paper by Grinker in *The Journal of the American Medical Association*.[4] The picture is vivid and terrible, a gross caricature of the reactions seen in civil life. As one would expect, the fear reactions are the commonest. Among many variations, three types of severe anxiety states may be picked out. There is that of the patient who is brought into the hospital shaking and looking terrified; his pulse is rapid and his blood pressure high; he sweats, has wide palpebral fissures and dilated pupils. There are coarse tremors, and speech is often a pathetic stutter. Startle reaction is marked, and attacks of laughing and crying, or of dashing about, may occur. Another clinical picture is that of somatic disintegration, in which the patient's condition may simulate Parkinson's syndrome or catatonic dementia precox because of the peculiar postures and motor disturbances. The face may be masklike and the limbs rigid and tremulous while the patient stands semifixed, sometimes with the hands below the knees; the gait may show propulsion. He may drool saliva, hold food for a long time in his mouth and have only gurgles and giggles for language. The behavior is childish and fearful and seems to represent a regression from adult integration.

A third type of severe anxiety state, less dramatic but more common, is stupor, in which the patient lies in bed staring vacantly. Many patients recover rapidly without treatment, passing through a stage of mutism to stammering speech and then fairly normal behavior with gaps in the memory. When a patient tries to overcome the amnesia, headache, dizziness and symptoms of anxiety may appear.

Milder anxiety states are more common than these three and are more like what one has seen in civilian life, with tremor, weakness, palpitation and fuguelike states in which the patients may wander away and be lost. They are tense and restless and sleep badly, often experiencing terror in battle dreams. After a few days they become quieter and then may insist that they can go back to their units, but a sudden noise will precipitate their symptoms all over again.

The cases of visceral expression of anxiety are abundant. Gastrointestinal symptoms predominate, such as anorexia, pain, belching and diarrhea. Enuresis is common. The "effort syndrome" ("soldier's heart"), so common in the last war, has been seen infrequently by these authors. Hysteria with conversion symptoms is rare. The patients observed have had the usual monoplegias, hemiplegias, pains and anesthesias, along with the typical indifference to their symptoms that sometimes caused medical officers to diagnose them as malingerers.

1. Sargant, W. W., and Slater, E.: Acute War Neuroses, Lancet **2**:1, 1940.
2. Murray, J.: Psychiatric Aspects of Aviation Medicine, Psychiatry **7**:1, 1944.
3. Grinker, R. R., and Spiegel, J. P.: Management of Neuropsychiatric Casualties in the Zone of Combat, in Solomon, H., and Yakovlev, P. I.: Manual of Military Psychiatry, Philadelphia, W. B. Saunders Company, 1944, chap. 35.
4. Grinker, R. R.: Treatment of War Neuroses, J. A. M. A. **126**:142 (Sept. 16) 1944.

Treatment of the patients suffering from these disorders depends, first of all, on good diagnosis. Inexperienced officers have frequently mistaken the more severe reactions for schizophrenia and looked on them as hopeless. Early recognition and sorting out are essential. The patients must be divided into: (1) those to be kept in the forward zones and returned to combat and (2) those that must go back to the general hospital. If exhaustion, hunger and thirst are important factors, quick sedation and rest with warmth, comfort and food will do much. Add to this encouragement and making much of the ideal of getting back to one's unit, and many of the patients are able to return to the front in a few days. When the anxiety is more severe the patient will not respond to this simple treament and will have to go to the rear for exploratory therapy. The story of how sedative drugs may be used to make accessible repressed memories is one of the most interesting chapters in the medical history of this war. Of course it is not new; Lindemann [5] wrote about it in 1930, and others since then have tried out the method in civil practice and found it only moderately useful. Various drugs have been employed, and especially useful have been sodium amytal, sodium pentobarbital, sodium evipal, pentothal sodium and hyoscine hydrobromide. The one most used just now is pentothal (sodium ethyl-[1 methylbutyl]-thiobarbituate). The method is variously known as "narcosynthesis," "narcoanalysis" and "hypnonarcoanalysis." The description of the treatment as given by Grinker and Spiegel is so good that I quote:

> The patient is isolated in a semidarkened room and is told that he is going to receive an injection which will make him sleepy. The drug is then injected in the antecubital vein at a slow rate (0.1 gm. per minute) while the patient is asked to count backwards from the number 100. Shortly after the counting becomes confused and before actual sleep is produced, the injection is discontinued. If the patient is mute or stuporous and, therefore, cannot count, a corresponding depth of narcosis must be estimated from the tonus of the eyelids and the pupillary reflexes. In rare instances the injection is difficult because of violent tremor of the arm. In almost every case there is some increase in the symptoms of anxiety as the injection is initiated. As it proceeds, however, the tremors disappear, and the patient becomes quiet. . . .
>
> . . . The patient is told in a matter-of-fact manner that he is on the battlefield, in the front lines. Depending upon the amount of known history, specific details are added corresponding to the actual situation at the time of the trauma. . . . The amount of such stimulation which is necessary to start the patient talking varies tremendously. Some react with the first few words and launch into a vivid account of the action. Others resist for varying periods, and when such resistance is maintained, the stimulation is made more dramatic and realistic. The therapist plays the role of a fellow soldier, calling out to the patient, in an alarmed voice, to duck as the shells come over, or asking him to help with a wounded comrade. Persistence is rewarded in almost every case by an account of the scene in progress.
>
> It is impossible to describe the varied reactions during a pentothal narcosynthesis. Some patients act out the traumatic parts of the battle scene. If this is their reaction, they are allowed to get out of bed and to wander about the room looking for a slit trench, a lost friend, the Command Post, or whatever the piece of action in hand calls for. Some live through the scene verbally and emotionally without the production of much motor activity. They talk to unseen buddies, wince at unheard explosions, bury their heads under the pillow when the shells come close and flatten themselves out on the bed as if they were in the bottom of their foxhole.
>
> It is electrifying to watch the terror exhibited in the moments of supreme danger such as at the imminent explosion of shells, the death of a friend before the patient's eyes, or the absence of cover under a heavy dive-bombing attack. The body becomes increasingly tense and rigid; the eyes widen, and the pupils dilate, while the skin becomes covered with perspiration. The hands move about convulsively, seeking a weapon, or a friend to share the danger. Breathing becomes incredibly rapid and shallow. The intensity of the emotion sometimes becomes more than the patient can bear and frequently at the height of the reaction, there is a collapse and the patient falls back in bed and remains quiet for a few minutes, usually to resume the story at a more neutral point. . . .
>
> . . . Other patients in whom there has been amnesia without much overt anxiety become suddenly blocked in the account of their experience as they approach the moment of trauma. As the anxiety begins to appear in anticipation of the traumatic scene, they cease talking and resume their characteristic defenses; they don't know what happened next. At this point the therapist applies pressure, demanding and forcing the patient to proceed. More than one session of narcosynthesis may be necessary to uncover the trauma. . . .
>
> During the time that the patient is thus wrestling with his traumatic experiences, the therapist plays an active or passive role in the performance to the degree required by the situation. No attempt is made to produce a hypnotic situation. The therapist remains as a vague background figure from which vantage point he can step into other roles as it becomes necessary. Some patients, especially those with only mild anxiety, good personality, and good contact with reality, are aware of the Medical Officer's presence throughout the treatment. They realize that they are telling the story to him and rely upon him only for emotion. In a severe case, however, in which there is much "living through" of the experience in the present tense, the patient is actually plunged in the battle situation. Here the Medical Officer is called upon to play a variety of roles. When the patient becomes convulsed with the violence of the terror, he must step in as a protective and supporting figure, comforting and reassuring the patient, and encouraging him to proceed. . . .
>
> When the initial problem is one of overcoming a somatic symptom such as mutism, deafness, or paralysis, the therapist may be required to adopt an authoritative role and command the patient to talk, to hear, or to move his limbs. Such direct interference is not always necessary. As the anxiety related to the traumatic situation emerges the symptom disappears spontaneously. A

5. Lindemann, E.: Psychopathological Effect of Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **28**: 864, 1931.

patient with a severe conversion symptom, under pentothal may begin to talk about his experiences in a calm, detached manner, but as he progresses, increasing quantities of anxiety are liberated. The somatic symptom disappears as the appropriate emotional reactions are liberated.

After this active therapy is finished psychotherapy by interview is kept up until the patient is fit for return to limited duty. Few of the patients who are sent back to general hospitals ever return to their units and the front lines.

Although I admire this paper by Grinker and Spiegel, so much that I review it at length and quote from it extensively, I do not agree with all the statements and implications. They state emphatically and without reservation that *"war neuroses are caused by war;* any one, no matter how strong or stable, may develop a war neurosis under proper circumstances." This assertion is apparently made in order to rid the psychiatrists of the subversive idea that war neurosis may be a breakdown based on "constitution or previous or latent neurosis." If they believed this they would "have a pessimistic therapeutic attitude," and "the quicker psychiatrists relinquish this idea the sooner they will achieve therapeutic success." On the same page the authors say that "the psychoneurotics crack up under mild battle stimuli."

Other writers on war neurosis do not agree with Grinker and Spiegel; for example, Sargant [6] says that the war has forced on him the recognition of the constitutional nature of much war neurosis, and Henderson and Moore [7] believe that war neurosis was "made in America" and predetermined before the man entered the service. I believe that some constitutional weakness and some tendency to neurosis are almost universal. It is a matter of degree and type of weakness that determines whether a man can stand much or little battle stress. Of course, it is desirable to get rid of the harmful, moralizing attitude that men who break with psychoneurotic symptoms are "weaklings." Grinker and Spiegel are probably right in saying that the terrors of modern war may break the best of us. I merely insist that the "best of us" have constitutional inadequacies and neurotic possibilities, and that recognizing this fact need not make the physician pessimistic about success in therapy.

This brings up the fact that there is no good and acceptable definition of "neurosis"—for the simple reason that no one knows what neurosis is. Grinker and Spiegel take war neurosis "in simple terms" to be "the effect of an interaction between the dynamic forces of anxiety and the protective devices of the ego." Translated into American, this means to me merely that a man uses the sum total of his personality to combat fear, and if he fails, he breaks. As for what neurosis actually is, one must at present take a descriptive point of view, because the cause is unknown. Freud,[8] who made such a great contribution to the understanding of the psychogenic factors in neurosis, believed that behind the psychologic disorders were humoral and constitutional troubles which would eventually be understood and lead to medical therapy. Other authors accent the constitutional weaknesses of the neurotics,[9] and some of Freud's followers insist that neurosis is entirely psychogenic. I believe that all one can now say about classification is that neurotic patients are those who suffer from a variety of symptoms which largely group themselves into syndromes well known as "nervousness," "anxiety attacks," "phychosomatic reactions," "reactive depression," "hysteria," "obsessive and compulsive reactions" and "hypochondriasis." The new war experience adds to this list the reactions that have been described here, most of which if seen in civil life one would call "psychotic" until one was surprised by the favorable outcome. In fact, the division of mental disorders into "neurotic" and "psychotic" is arbitrary and fallacious.[10]

Some headway has been made in understanding the psychogenic factors in the different neuroses. Freud pointed out various "defense mechanisms" used by neurotic patients and to some extent made his diagnosis on the basis of what sort of "mechanism" the patient employed. Unfortunately he did not make a new nomenclature for the neuroses to fit the psychologic origin, but used old terms in a new way, always a confusing procedure. Nevertheless, some psychologic reactions seem to be somewhat typical of different types of neurosis; for example, the simple expedient of forgetting in the typical hysterical amnesia, the guilt feelings so common in reactive depression and the preoccupation with rituals to ward off anxiety in the compulsive neurotics. Until there is more knowledge about heredity and the psychologic and physiologic

6. Sargant, W.: Physical Treatments of Acute Psychiatric States in War, War Med. **4**:577 (Dec.) 1943.

7. Henderson, J. L., and Moore, M.: Psychoneuroses of War, New England J. Med. **230**:273, 1944.

8. Freud, S.: Gesammelte Schriften, Vienna, Internat. Psychoanalyt-Verlag, 1928, vol. 11, p. 362.

9. Symonds, C. P.: Anxiety Neurosis in Combatants, Lancet **2**:785, 1943. Debenham, G.; Hill, D.; Sargant, W. W., and Slater, E.: Treatment of War Neurosis, ibid. **1**:107, 1941.

10. Cobb, S.: Borderline of Psychiatry, Cambridge, Mass., Harvard University Press, 1943.

mechanism involved in "neurosis," little progress can be made in classification and prevention. Therapy can still go ahead along psychologic lines because psychotherapy has empirically proved itself of value.

EXPERIMENTAL NEUROSIS

There is hope of increased progress in the understanding of the neuroses because of experimental work on animals that seems to throw some light on the physiology and psychology of these conditions. The first step, that of producing in animals a disorder analogous to that seen in man, was accomplished by Pavlov twenty years ago, but did not reach the attention of physicians until Liddell began publishing his pioneering work on "experimental neurosis" in 1927. Liddell and his colleagues have carried on this research up to the present time, and a summarizing paper [11] in Hunt's "Personality and the Behavior Disorders" (chapter 12) brings the subject up to date. Not only has Liddell corroborated and expanded Pavlov's observations, but he has shown that some of the concepts were wrong. In the first place, Pavlov was a physiologist who was trying to study one set of functions in the dog in a scientific and impersonal way. He disliked psychology and felt that an exact science must avoid such multiple variables and loose concepts as the psychologists used. Thus he believed that his dogs in the dark and sound-proof room, where they stood in harness on a table and reacted to carefully graded stimuli, day after day, were giving him examples of reflex action cut off from all extraneous stimulation by the environment. It has been one of Liddell's contributions to show that "Pavlov's classical method of the conditioned reflex was not an impersonal observational procedure, but a traumatizing procedure." The very restriction of environment by taking the animal into an enclosure in a small room, the lack of noise, the loneliness, the standardization of procedure and the monotony all affected the animals by limiting their freedom and changing their habits. Not only did their reactions become abnormal while responding to laboratory procedure, but their whole way of life in the barnyard. Liddell has case histories of sheep trained to the laboratory for periods of five to fourteen years. Goats and pigs were also used, the latter being the most resistent to the narrowed environment. But all could be trained with time and patience to stand willingly in the Pavlov frame and wait for the stimuli and rewarding food. The difficult differentiations given to the animals after they were well trained were no doubt the final precipitants of the "neurotic" reactions, but they were the "last straw" and not the sole cause as Pavlov thought. Liddell says:

> The situation, as we now view it, appears as follows. Domestication itself imposes upon the animal restrictions and pressures, a hierarchy of them, beginning with the simple physical restraints imposed by the fenced-in area within which the animal lives. It must be recognized that its food is not sought after but is supplied at stated times. It is forced to associate with other animals of its own species and of other species. Crises involving self-defense, reproduction, and food arise from time to time. Then again, the animal assumes a submissive relation to the attendant and experimenter. From this account it can be seen that the perplexing problems which face the animal in the conditioned reflex laboratory represent restraints and pressures situated at the apex of a pyramid. Progressive restriction of liberty and correlative increase in pressures (similar to those exerted by society on the human individual) extend from the wild state, through domestication, to the too refined training of the laboratory.
>
> As training progresses the animal's behavior becomes more predictable and impulsiveness gives place to skill. That is to say, the animal comes to stand quietly in the Pavlov frame and, at the signal intimating the coming shock to the forelimb, it no longer struggles to escape. Instead, it makes a deliberate postural adjustment preparatory to executing a precise series of flexion movements with the member to which the shock is about to be applied.
>
> The daily period of self-imposed restraint to which the animal is subjected in the conditioning laboratory, together with its relinquishment of initiative and spontaneity within the testing period, we now believe, lays the foundation for the pathological outcome of long-continued training. Yet this self-imposed restraint is not of itself sufficient to lead to disturbed behavior.

Sheep and goats subjected to a conditioning regimen that caused them to flex a limb periodically in response to a buzzer noise, after many repetitions would delay the response and prepare the posture of the limb for it, and eventually there would develop a stiffening and motor incapacity of the limb that might last for years. The resemblance to human hysteria is obvious.

Gantt [12] has recently published a monograph on the "origin and development of artificially produced disturbances of behavior in dogs." He brings out many of the points discussed by Liddell, but his dogs were less confined in the experimental situation and the relationship between dog and experimenter was obviously important, even more so than in the experiments of Liddell in which he also appreciated the importance of the "rapport" between animal and experimenter.

Gantt's monograph begins by showing that the method of conditional reflexes is a sound one and brings psychobiology to a high level of scientific

11. Liddell, H. S.: Conditioned Reflex Method and Experimental Neurosis, in Hunt,[12] chap. 12.

12. Gantt, W. H.: Experimental Basis for Neurotic Behavior, New York, Paul B. Hoeber, Inc., 1944.

accuracy at which experimental data may be expressed in mathematical formulas. He shows clearly, however, that when one deals with the higher cerebral functions, such as conditioning, generalization concerning responses made as if they applied to all higher mammals or even to one species are fallacious. The problem becomes individual; each animal responds differently at these higher levels, because each animal differs in hereditary makeup and life experience.

Disturbances in behavior that resemble human "neurosis" can be brought about in animals by natural emotional shocks, such as parturition in female dogs, a male dog's being near a female in estrus, fighting and threats to life, as in the famous case in which Pavlov's laboratory was flooded and the dogs nearly drowned. The monograph, however, centers on the acute disturbances artificially produced by the conditioning experiment. The general training situation is recognized by Gantt as abnormal and leading to "neurotic" reactions, but specific experimental procedures are especially discussed, such as the simultaneous excitation of the unconditioned reflexes or the making of a more and more difficult differentiation between two conditioned stimuli. For example, a dog is taught to differentiate between a metronome at the rate of 60 and another at the rate of 144; one means to him "food" and the other "no food." If these signals are given at seven minute intervals he reacts normally and appropriately, but if they are given too close together the dog makes mistakes, does not salivate regularly and then has spells of dyspnea and finally falls asleep on the stand. The dog, "Nick," is the most interesting of the subjects described by Gnatt. This animal was trained and precipitated into "neurotic" behavior by causing him to attempt to differentiate between a pair of musical tones.

Nick was a mongrel male born about 1929 or 1930, weight about 12 kg. He was introduced into the laboratory in early 1931 and kept in the paddocks with the other dogs. For about a year before any work was done on him he was brought into the experimental room for casual observation. Nothing was noted then that impressed one as remarkable; in fact, he was selected with Fritz and Peter for laboratory work, as being, according to general appearances, normal. He seemed to be lively and playful, perhaps even more companionable and easy to make friends with than other new dogs.

No careful and detailed examination was made on him prior to experimentation, but it is significant that casually and by the means of ordinary observation he appeared normal, as shown by selection for experiments requiring a normal animal. The contrast between the results of casual observation and the subjection to the rigidly controlled and delicate measurements in the routine of the laboratory deserves emphasis. *It is only by the latter method that we can detect the individual which will show a breakdown under stress.* The early symptoms seen in the laboratory situation which gave us a clue to the constitutional instability were in Nick (1) refusing to eat, (2) the absence of inhibition of the conditional reflex when the differentiation became hard, the slight conditional reflex at first, and the easy setting in of inhibition, (3) the lack of differentiation, (4) the striking increase of muscular activity and restlessness.

It is remarkable in Nick not only that the nervous symptoms have continued for ten years without repeating the original conflict but that the spread to the urinary and sexual systems did not occur till after 1935, several years after the conflict. That they were related to the conflict is shown by their appearance only in the experimental environment and other relationships to the original stimuli, as will be discussed.

Nick became excited and restless when the environment of the experimental room, or any part of it, was brought to his attention. The experimenters were an important element, and he ignored and gave cold treatment to Gantt even when he had a long rest on the experimenter's farm. Other symptoms were motor tensions, vocalizations, palpitations, dyspnea and anorexia with refusal of food that was in any way reminiscent of the experimental room. Most interesting of all, however, were the sexual reflexes that developed slowly and lasted for years. Erections and even ejaculation would occur when Nick was brought into the experimental room. When he was tested by local application of electrical stimulation to the genitalia it was found that his time of beginning of erection was slightly decreased, the time of duration of erection was greatly reduced and the latent period of ejaculation was shortened. In other words, the disturbing situation in the laboratory gave Nick a syndrome resembling human ejaculatio praecox.

For more details the monograph of Gantt and the papers of Liddell must be consulted. The items here picked out for discussion clearly indicate that a good beginning has been made in the experimental approach to neurosis. Of especial interest (in relation to the discussion under "Neuroses and the War" about the constitutional factor in neurosis) is the agreement of Pavlov, Liddell and Gantt on the importance of the "premorbid personality" of the animal, his lability or stability, which according to Gantt can be tested only by special methods and should not be left to general clinical impression as to whether an animal is "nervous" or not.

PERSONALITY

The war, with its need for evaluation of men, has led to a great increase in studies of personality. Leaders must be chosen; men must be picked for aviation, for military government and for a hundred other jobs. This has now brought forth a host of methods and theories, bad and good. The publication of a two volume handbook on "Personality and the Behavior Dis-

orders" [13] this year has given a sound basis from which students of "personology" may start. The book was put together and edited by Professor Hunt, of Brown University. In volume I there are thirty-five chapters by different authors, taking up theoretic approaches to personality, methods of assessing personality, experimental behavior disorders, hypnotism, heredity and other biologic determinants of personality. In the next volume personality is taken up in relation to infancy and childhood experience, adolescence and culture. The main types of behavior disorder are described by different psychiatrists, and special methods are discussed. The articles are remarkably sound and readable, giving historical summaries and new points of view. There is enough difference of opinion to add spice and show that much is not yet settled. For the physician this is a book with many hours of profitable and enjoyable reading.

NEUROLOGY

The war has also affected adversely the production of neurologic papers. Many of the journals in this specialty are much smaller than they previously were, and some of them have ceased publication altogether. The papers are shorter, and, although many of them are of immediate interest in relation to the war, there is less serious and consecutive work to be reported. Of course, a great deal of research is going on in the armed forces and for the war effort, but this is largely restricted and cannot be published and reviewed at present.

METABOLISM OF THE BRAIN

In looking through the recent neurologic literature, it is obvious that there has been an increase in interest in the subject of cerebral metabolism, especially the use of oxygen by the brain. This has been stimulated in the first place by the work on insulin shock therapy and in the second by the needs of aviation medicine, in which states of anoxia or hypoxia are common. Rossen, Kabat and Anderson [14] have reported new methods for observing the effect of occlusion of the carotid arteries to cause sudden and temporary cerebral anoxia. They made a cuff that fitted around the neck which could be inflated to a pressure of 600 mm. of mercury within one eighth of a second. They examined both normal subjects and schizophrenic patients and showed that loss of consciousness in young men appeared six and eight-tenths seconds after the occlusion of the circulation. This coincided with the appearance of slow waves in the electroencephalogram. Former experimenters had believed that unconsciousness did not occur as rapidly as that and had given such figures as eleven and twenty-one seconds. Gurdjian, Stone and Webster [15] studied the effects of varying degrees of hypoxia on the metabolism of the brain. It is well known that lactic acid and the decomposition of phosphocreatine occur when there is oxygen deprivation in the brain. These authors designed experiments to find the critical oxygen levels at which these changes appear. Dogs were exposed to breathing mixtures low in oxygen for periods of fifteen to sixty minutes. At the level of 11 to 13 per cent of oxygen in inspired air, the lactic acid in the brain increased. This occurred when the oxygen saturation in the arterial blood was between 55 and 65 per cent and that of the venous blood was between 28 and 43 per cent. Decomposition of phosphocreatine began when the oxygen level in the inspired air reached 7 per cent. If the animal was allowed to rebreathe air, resynthesis was complete in about five minutes.

Joseph Wortis [16] studied cerebral oxidation by means of the Barcroft-Warburg manometer. The material was minced whole brain tissue of adult white rats. He was able to show that the uptake of oxygen had a sharp rise for the first six hours, with a flattening off thereafter. If a small amount of serum was added to the immersion fluid, the oxidation continued at a practically constant rate for the duration of the experiment and did not flatten off at six hours. This might mean that there is in blood serum some essential factor of the oxidative enzyme system.

Chesler and Himwich [17] have studied the glycogen content of the brain and found that each part of the central nervous system possesses a characteristic concentration of glycogen. These values were shown to be relatively constant. In their most recent paper they report trying the effect of insulin hypoglycemia on the glycogen content of parts of the central nervous system of the dog. It was observed that the decrease in glycogen began in the corpora quadrigemina, followed by the cortex, thalamus, cerebrum and medulla, in that order.

13. Hunt, J. M.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944.

14. Rossen, R.; Kabat, H., and Anderson, J. P.: Acute Arrest of Cerebral Circulation in Man, Arch. Neurol. & Psychiat. **50**:510 (Nov.) 1943.

15. Gurdjian, E. S.; Stone, W. E., and Webster, J. E.: Cerebral Metabolism in Hypoxia, Arch. Neurol. & Psychiat. **51**:472 (May) 1944.

16. Wortis, J.: Effect of Serum on Survival Time of Brain Tissue and Revival of Cerebral Oxidation, Arch. Neurol. & Psychiat. **51**:176 (Feb.) 1944.

17. Chesler, A., and Himwich, H. E.: Effect of Insulin Hypoglycemia on Glycogen Content of Parts of the Central Nervous System of the Dog, Arch. Neurol. & Psychiat. **52**:114 (Aug.) 1944.

These papers are indications of the interest in brain metabolism and of the advances that are being made in that line. To bring this work into relationship with the histopathology of the brain, one has only to turn to the recent experiments of Hurst.[18] He gave daily sublethal doses of potassium cyanide to animals and found that after large doses microscopic sections of the brain showed areas of cortical necrosis. With smaller doses given over a longer period, there would be patches of necrosis in the white matter and loss of myelin. With the smallest doses,[19] given over periods of four months or more, there were massive areas of demyelination reminding one of the lesions of Schilder's diffuse sclerosis. These lesions seem to be of the same age everywhere, and because cyanide is known not to accumulate in the tissues, one must conclude that the effect is due not to an accumulative toxin but to repeated attacks of histotoxic anoxia. Somewhat similar lesions had been caused some years before by Ferraro.[20] Hurst's work elaborated on the earlier experiments and succeeded in producing lesions with a number of histotoxins. Besides the potassium cyanide, he used sodium azide, hydroxylamine, ethylcarbanate (urethane) and pentobarbital sodium. It was his belief that these drugs inhibited one or another of the various enzyme systems and that the lesions came from the resulting lack of oxygen.

The common demyelinating diseases, especially the noninfectious encephalitides, multiple sclerosis and Schilder's disease, are all of unknown cause. These advances in the understanding of cerebral metabolism and of the effect of inhibiting oxygen uptake may eventually lead to a better understanding of the origin of these obscure conditions.

18. Hurst, E. W.: Experimental Demyelination of the Central Nervous System, Australian J. Exper. Biol. & M. Sc. **18**:201, 1940.

19. Hurst, E. W.: Experimental Demyelination of the Central Nervous System, Australian J. Exper. Biol. & M. Sc. **20**:297, 1942.

20. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267, 1933; Experimental Toxic Encephalomyelopathy, Arch. Neurol. & Psychiat. **29**:1364 (June) 1933.

News and Comment

PENICILLIN AND WARFARE

Supplement to the July 1944 Issue of the *British Journal of Surgery*

A supplement to the July 1944 issue of the *British Journal of Surgery* presents a symposium on Penicillin in Warfare, including reports of clinical experiences of a preliminary nature in the treatment of recent war wounds in the field with penicillin. It contains a foreword by Major General L. T. Poole on the successful employment of penicillin in the most forward surgical units as a prophylactic against wound sepsis. General Poole says that in some instances a long interval must elapse before definitive surgical procedures can be undertaken and that penicillin can be used to bridge this gap and delay, modify or even prevent the development of sepsis.

Florey and Jennings point out that the substance is the most powerful antibacterial agent which has been brought into clinical use and that it will completely inhibit the growth of the most sensitive organisms, such as gonococci and staphylococci, when diluted at least 1 : 500,000,000.

Lieutenant Colonel Jeffrey discusses the specific action of penicillin against the common bacterial invaders of war wounds (staphylococci and clostridia in the early stages and streptococci in the later stages) and expresses the opinion that it is the most effective and least harmful agent yet discovered. The drug has three main spheres in war surgery: (1) to prevent early infection of a wound; (2) to control infection in the first two weeks—this is the sphere in which the greatest value can be expected from penicillin—and (3) to combat sepsis in the later stages.

Lieutenant Colonel Bentley reports on a series of 200 consecutive casualties with flesh wounds treated by early secondary suture with local application of penicillin and states that primary healing was obtained in 190 (95 per cent).

Lieutenant Colonel Brown reports much the same results. He feels that the results are so good and the period of morbidity so lessened that all soft tissue wounds, however small, should be sutured with the aid of penicillin. He warns, however, that penicillin has in no way replaced and can never be a substitute for thorough primary surgical treatment.

Furlong and Clark state that penicillin failed to control sepsis fully and did not diminish the incidence of chronic infection in open fractures of the femur. They therefore stress that penicillin is not a substitute for surgical intervention and that the greatest care and attention must be given to surgical technic and to fundamental surgical principles.

Jeffrey believes that penicillin has a definite place alongside surgery and antiserum in the treatment of gas gangrene.

D'Abreu and his associates have been particularly impressed with the capacity of the pleural cavity to retain instilled sodium penicillin for as long as three days. They recommend that in the forward areas the attempt to prevent infection of hemothoraxes should consist in thorough aspiration combined with instillations of penicillin, which they feel would offer the best hope of preventing the present high rate of hemothorax infections seen in the theater of war.

Major Robinson, of the United States Army, reports on 1,000 patients with sulfonamide-resistant gonorrhea treated with penicillin, 94.7 per cent of whom were free of gonorrhea after one course of treatment of 100,000 units given intramuscularly in 10,000 unit doses every hour or in 20,000 unit doses every three hours. The remaining patients required a second course of penicillin, varying from 100,000 to 150,000 units.

Wise and Pillsbury, of the United States Army, confirm in general the report of Mahoney and his associates on the rapid spirocheticidal effect of penicillin in human beings, the prompt regression of early lesions and the absence of significant reaction to treatment.

Book Reviews

Infectious Anemias Due to Bartonella and Related Red Cell Parasites. David Weinman. In Transactions of the American Philosophical Society, 1944. New Series, Volume 33, Part III. Price, $1.25. Pp. 108. Philadelphia: American Philosophical Society, 1944.

Human bartonellosis, although confined today to areas within Peru, Colombia and Ecuador, is a disease of great clinical and epidemiologic interest. It is unique in that hitherto it has not spread from these Andean regions, a feature which doubtless depends on its low infectivity and the importance of the insect vector, a species of phlebotomus fly, in transmission to man. Weinman's monograph offers in detailed and authoritative fashion what is known of this interesting malady. The two manifestations of human bartonellosis, namely, a severe febrile anemia and a benign eruption, are separately presented in their varied forms and complications. Much is still obscure in the epidemiology of the disease. There is no doubt that all naturally contracted infections are conveyed by the sandfly; direct contagion is rare, although Carrion, at the cost of his life, proved that direct inoculation of infectious material is successful and, as early as 1885, showed that the infectious agents of verruga peruana and Oroya fever are the same.

Hemobartonella and animal bartonellosis are presented in the second chapter. Infectious anemias of animals caused by micro-organisms parasitizing the erythrocytes seem to be fairly common; they comprise three genuses: Grahamella, Eperythrozoon and Hemobartonella. With the possible exception of Eperythrozoon, none of them affects man; however, they are interesting in that they belong, with Bartonella, in that relatively small class of infectious agents that grow in or on red cells.

Weinman describes, in the third chapter, the species of Eperythrozoon and the diseases they cause in animals. These pathogens affect mice and other rodents, and sheep and cattle. Splenectomy precipitates violent infections. Organic arsenicals rapidly sterilize infections with Eperythrozoon and Hemobartonella, but they have no effect on infections caused by Grahamella and little or none on bartonellosis of man.

The public health aspects of human bartonellosis are discussed in the last chapter. Severe epidemics with a high mortality rate have been observed; in one instance 4 per cent of the population died from the disease in one year. The disease is especially violent among newcomers to endemic areas and in new populations in nonendemic zones. Prior infections seem to confer some degree of resistance to an individual; however, persons who have recovered may act as carriers for months or perhaps years. Public health measures must prevent contact between sandflies and man. Since these insects are night biters, these measures may include: (*a*) leaving the endemic region at nightfall, (*b*) use of bed nets and (*c*) construction of fly-proof buildings. The best measure of all is the removal of the entire population from the infected areas. Economic considerations and the habits of the people will make these measures hard to apply.

This publication is recommended to all who are interested in the infectious anemias of man and animals. It contains much information originally recorded in foreign journals; more important, however, is that this and much other information have been carefully assembled and presented in an orderly and systematic fashion.

Clinical Tropical Medicine. By twenty-seven authors and edited by Z. Taylor Bercovitz, M.D. Price, $14. Pp. xvii + 957, with 121 illustrations and 20 plates. New York: Paul B. Hoeber, Inc., 1944.

This volume, written with good editorial cohesion by a group of experts, covers the field of tropical medicine in an altogether satisfactory manner. It is comprised of eleven sections, which seem to divide the broad subject of the book in a logical way. Thus diseases characterized by diarrhea or caused by protozoa, spirochetes or rickettsias or of any other known cause are grouped together. And since the book is designed for the clinician, all the diseases described are considered in the uniform style that a clinician likes, first with a historical note and then with succeeding paragraphs on etiology, epidemiology, pathology, symptomatology, diagnosis, prognosis, treatment and prevention. At the end of each chapter is a short bibliography.

All the authors are well known and are thoroughly familiar with the subjects allotted to them. The editor has managed to make the text read as if it were written by a single person. The illustrations, on the whole, are clear and help materially in elucidating the appearance of lesions or parasites which will be no more than names to many readers.

Dr. Wilbur Sawyer, of the International Health Division of the Rockefeller Foundation, has written a foreword. He points out that most American physicians and medical students have until now felt no urge to familiarize themselves with exotic and tropical diseases. War, however, has suddenly brought a departure from this medical isolationism. There is now a pressing demand for authoritative and practical instruction in the treatment and prevention of diseases of the warm countries.

This book, therefore, well put together as it is, is certain to be useful to a wide variety of readers. It is less bulky and more easy to manage than the larger works on tropical medicine; at the same time it is a good deal broader and more comprehensive than are the epitomes which have appeared recently. It deserves a high degree of popularity.

The Urinary Tract: A Handbook of Roentgen Diagnosis. By H. Dabney Kerr and Carl L. Gillies. Price, $5.50. Pp. 320, with numerous illustrations. Chicago: The Year Book Publishers, Inc., 1944.

The Year Book Publishers have embarked on the manufacture of a series of short handbooks dealing with roentgenologic diagnosis. This volume, which is listed as sixth in the series, considers the urinary tract.

It is a workmanlike affair copiously illustrated with excellent reproductions of films. There are four major divisions of the subject matter: the kidney, the ureter, the bladder and the urethra. The text describes these anatomic units from a radiologist's point of view, describing first what is considered their normal visualization and then various deviations from the normal.

On pages opposite to the text are reproduced characteristic roentgenograms, which illustrate with delightful clarity the points in the text that appear to deserve greatest emphasis.

The book is so clearly written that it is easily read, and the illustrations are particularly good. On the whole, this small handbook is bound to be a popular adjunct to any hospital library. It will be useful to students and interns and to such inquisitive staff members as still attempt to see for themselves how the master radiologist interprets his findings in facing the baffling diagnostic problems afforded by diseases of the genitourinary tract.

Clinical Syphilology. By John H. Stokes, Herman Beerman and Norman R. Ingraham, Jr. Price, $10. Pp. 1332, with 911 illustrations. Philadelphia: W. B. Saunders Company, 1944.

Stokes's "Clinical Syphilology" has really become an institution in American medicine in the sense that there is no other work which fully takes the place of this outstanding treatise. Dr. Stokes's lucid and vivid style relieves the text of the monotony so to be dreaded in large monographs. Every phase of the subject is thoroughly gone into—bacteriology, clinical features, theory and practice of treatment and public health aspects. The numerous illustrations, tables and summaries enrich and enliven the text.

The fact that Stokes has worked in such harmony with other outstanding American syphilologists makes what he has to say even more impressive, since the work represents, as the writer says in his preface, to some extent a synthesis of experience. It is somewhat appalling to find that 1,300 pages must be devoted to the discussion of one disease, even though it is a very important one. As Dr. Stokes optimistically points out, it is to be hoped that penicillin or some similar agent will so alter the situation as materially to simplify the whole subject.

Heart Disease. By Paul Dudley White, M.D. Third edition. Price, $9.00. Pp. 1025. New York: The Macmillan Company, 1944.

The third edition of this standard work on diseases of the heart needs no introduction to the medical profession. It has been for nearly fifteen years probably the most popular book on cardiac disorders that the medical profession makes use of in teaching and in practice. It is almost encyclopedic in content; it is complete in every respect. Only one or two criticisms may be pertinent. In the first place, the list of references after each chapter is extensive. To the student, at least, a few well selected references might be of greater value than a list of some thirty to one hundred articles. Many of these articles are good, but some are better than others, and only the best should be listed for the uncritical reader or the tyro.

Another minor criticism is the weight of the book, almost 3 pounds (1.3 Kg.), which makes for a great deal of difficulty in reading unless there is some kind of support other than the unaided arms. These criticisms are of minor importance and do not negate the essential value of this well written, authoritative, extremely detailed and comprehensive book on cardiac disease.

Proteins and Amino Acids: Physiology, Pathology, Therapeutics. Pp. 189, with 5 illustrations. Yonkers, N. Y.: The Arlington Chemical Company, 1944.

Although sponsored by the Arlington Chemical Company, this little book contains no advertising matter. It consists of a good practical summary of current knowledge about proteins and their breakdown products and metabolism. It should be a useful compendium for persons who wish to orient themselves as to the newer aspects of protein therapy in connection with surgical operations, burns and fractures.